Chapter 3

STUDY DESIGN

3.1 OBJECTIVES, DEFINITIONS, AND METHODS

AREDS is a multi-center cohort study designed to assess the clinical course, prognosis, and risk factors of AMD and cataract. As illustrated in Exhibit 3-1, the incidence and progression rates and risk factors of each disorder will be evaluated. Most of the risk factors will be assessed observationally. Additionally, the effects of pharmacologic doses of (a) antioxidants and zinc on the incidence and progression of AMD and (b) antioxidants on the incidence and progression of lens opacities will be assessed as part of a randomized clinical trial (Exhibit 3-2). Before randomization, participants will take part in a run-in period of at least 1 month, during which they will receive placebo tablets (Trial Medication) for daily intake.

This section describes the AREDS objectives, definitions, eligibility criteria and methods, and statistical considerations. Subsequent sections describe three design elements for achieving the AREDS objectives: the study of clinical course and prognosis, risk factors study, and the clinical trial. These last three sections are divided into cataract and AMD subsections within which the specific objectives, study populations, outcome variables, and statistical considerations are discussed.

3.1.1 Objectives

The primary objective of AREDS is to evaluate the clinical course and prognosis of cataract and AMD. This objective will be accomplished by collecting and assessing the data on approximately 4,600 AREDS participants aged 55 to 80 years, who, at the time of enrollment, may or may not have cataract or AMD or both. The information that will be collected and assessed is:

- Change in visual acuity
- Disease incidence
- Disease progression
- Risk factors

In order to describe disease progression, the study will refine and apply classification scales for lens opacities (cortical, nuclear, and posterior subcapsular) and AMD lesions.

Information on usual nutritional intake will be collected at baseline to evaluate potential nutritional risk factors for cataract and AMD. In addition, study participants will be assigned randomly to take one of the following Study Medications on a daily basis: placebo, antioxidants, zinc (copper added), or the combination of antioxidants and zinc. The objectives of this clinical trial part of the study are to:

1. Study the effects of high supplemental doses of antioxidants and zinc on the development of advanced AMD in a 2^2 factorial design.

2. Study the effects of high supplemental doses of antioxidants on the development and progression of lens opacities.

3.1.2 Definitions

The definitions adopted for lens opacities, small drusen, intermediate drusen, large drusen, advanced AMD, extensive drusen, AMD classification, and event photographs are given below.

3.1.2.1 Lens opacity. The presence and severity of nuclear, cortical, and posterior subcapsular (PSC) lens opacities will be determined by the grading of lens photographs according to the AREDS Lens Opacity Grading System (Exhibit 3-3). The following classifications are based on this grading system:

	Original	Rescaled
! Nuclear		
Absent or questionably present	grade 0.9 to 1.9	0.9 to 1.4
Present		
Very mild	grade 2.0 to 2.9	1.5 to 1.9
Mild	grade 3.0 to 3.9	2.0 to 2.9
Moderate	grade 4.0 to 4.9	3.0 to 3.9
Severe	grade 5.0 to 5.9	4.0 to 4.9
Very severe	grade 6.0 to 6.9	5.0 to 5.9
Extremely severe	grade 7.0 to 7.1	6.0 to 6.1

	% of standard area (5mm diameter)
! Cortical	
Absent or questionably present	0 - 5%
Present	
Early	6 - 25%
Late	>25%

	% of central area (2 mm diameter)	% of standard area (5 mm diameter)
! PSC		
Absent or questionably present	0 - 5%	<1%
Present		
Early	6 - 25%	1-4%
Late	>25%	>4%

Participants meeting the definition for early or late opacity of any type in at least one eye will be classified as having lens opacity.

3.1.2.2 Small drusen. Drusen < 63 microns (μM) in diameter located within 2 disc diameters of the center of the macula.

3.1.2.3 Intermediate drusen. Drusen ≥ 63 microns but < 125 microns in diameter located within 2 disc diameters of the center of the macula.

3.1.2.4 Large drusen. Drusen ≥ 125 microns in diameter located within 2 disc diameters of the center of the macula.

3.1.2.5 Advanced AMD. Atrophic or exudative neovascular changes of AMD that include one or more of the following:

(a) Definite geographic atrophy definitely or questionably involving the center of the macula (minimum diameter for a patch of atrophy to be classified as geographic is that of circle I_1, or 175 μM)

(b) Evidence suggesting exudative disease, including:
  (1) Serous detachment of the sensory retina
  (2) Subretinal hemorrhage
  (3) Retinal pigment epithelial detachment (PED) excluding drusenoid type (Chapter 15, Section 15B.7.3)
  (4) Disciform scar (subretinal fibrous tissue)
  (5) Scar of previous photocoagulation presumed to have been for treatment of choroidal new vessels (CNV).

3.1.2.6 Retinal pigment epithelial abnormalities consistent with AMD. One or more of the following:

(a) retinal pigment epithelial depigmentation definitely present within 1 disc diameter of the center of the macula (i.e., in the center and inner subfields of the standard grid)

(b) increased pigmentation of the RPE and/or retina within 1 disc diameter of the center of the macula if its total extent equals or exceeds standard circle C1 (125 microns in diameter)

(c) any definite increased RPE pigmentation within 1 disc diameter of the center of the macula if RPE depigmentation is at least questionably present within 1 disc diameter of the center of the macula

and absence of characteristics suggestive of some condition other than AMD.

3.1.2.7 Extensive drusen. "Extensive drusen" is defined separately based on drusen size.

(a) small: total extent of small drusen within 2 disc diameters of the center of the macula is greater than or equal to the area of a circle 125 microns in diameter, an area corresponding to a count of ≥15 small drusen in stereo photographs

and probably comparable to a count of 5 to 10 small drusen by ophthalmoscopy.

(b) intermediate: total extent of drusen is at least that of Circle I-2 (i.e., about 20 average-size intermediate drusen) if soft indistinct drusen are present or at least that of Circle O-2 (i.e., about 1/5 disc area, or about 65 average-size intermediate drusen) if soft indistinct drusen are absent

3.1.2.8 AMD classification. A four-category classification of participants is defined for AREDS based on the size and extent of drusen in each eye, the presence of manifestations of AMD, and visual acuity. Different event rates (Section 3.2.2.4) are expected in each category, and Clinical Centers have been assigned quotas for participants they are expected to enter into each category (Section 3.1.3.6). The AMD classification of participants is determined by the Reading Center from photographs. The first three AMD categories used in AREDS apply when neither eye has advanced AMD. The fourth AMD category applies when one eye only has evidence of advanced AMD, or has a visual acuity score of 73 letters or less with the decrease in vision attributable to AMD. The four categories are:

! AMD Category 1. Each eye has:
  (a) No drusen or small, nonextensive drusen
  (b) No intermediate drusen
  (c) No large drusen
  (d) No pigment abnormalities
  (e) No advanced AMD
  (f) A visual acuity score of 74 letters or more
  (g) No disqualifying lesions.

! AMD Category 2. At least one eye has one or more intermediate drusen, extensive small drusen, or pigment abnormalities associated with AMD, and neither eye has:
  (a) Large drusen
  (b) Advanced AMD
  (c) A visual acuity score of 73 or less
  (d) A disqualifying lesion.

! AMD Category 3. There are two types of AMD Category 3 participants.

  (A) At least one eye has one or more of the following:
    (1) One or more large drusen
    (2) Intermediate drusen, with total drusen area
      (a) At least that of Circle I-2 (i.e., about 20 average-size intermediate drusen) if soft indistinct drusen are present or
      (b) At least that of Circle O-2 (i.e., about 1/5 disc area, or about 65 average-size intermediate drusen) if soft indistinct drusen are absent

(3) Definite geographic atrophy not involving the center of the macula, and neither eye has any of the following:
(1) Advanced AMD
(2) A visual acuity score of 73 letters or less
(3) A disqualifying lesion.

or

(B) Only one eye meets the criteria specified above in part (A) and the fellow eye has either of the following:
(1) A visual acuity score of 73 or less not attributable to AMD, or
(2) A disqualifying lesion (listed in Section 3.1.3.2) considered to be uniocular.

! AMD Category 4. There are two types of AMD Category 4 participants.

(A) One eye has advanced AMD with or without visual acuity score of 73 or less, and with or without a disqualifying lesion considered to be uniocular, and the fellow eye has:
(1) A visual acuity score of 74 or more
(2) No evidence of advanced AMD
(3) No disqualifying lesion.

or

(B) One eye has reduced vision (< 74 letters) due to AMD, but no evidence of advanced AMD, and the fellow eye has:
(1) A visual acuity score of 74 or more
(2) No evidence of advanced AMD
(3) No disqualifying lesion.

3.1.2.9 Event photographs. Photographs of each eye are required to document the status of the lens (of phakic eyes) and fundus when the visual acuity score measured during a scheduled visit drops by 10 or more letters from the Randomization Visit score in either eye (Chapter 6). One set of event photographs is required for each eye to document the first decrease in visual acuity by 10 or more letters in that eye. Subsequent decreases do not require event photographs. Event photographs are required for all eyes regardless of AMD status at study entry.

3.1.3 Eligibility and Exclusion Criteria

Ocular and general criteria for eligibility in AREDS are defined in this section. In Phase II, the informed consent of all participants (including those who participated in Phase I) must be obtained at the Qualifying Visit and again at the Randomization Visit (Section 3.1.3.3 and the model informed consent forms in Appendix B). Eligibility for Phase I does not assure eligibility for Phase II, and consent for Phase I does not extend to Phase II. To be eligible for Phase II, participants must meet each ocular and general eligibility criterion but not meet any ocular exclusion criterion listed in the sections below.

3.1.3.1 Ocular eligibility criteria. Participants must meet the following visual acuity and media clarity criteria:

1. Visual acuity score at the Qualifying Visit for

   (a) AMD Category 1 or 2: 74 or more (Snellen equivalent approximately 20/32 or better) in each eye.

   (b) AMD Category 3: 74 or more (Snellen equivalent approximately 20/32 or better) in at least one eye with large drusen or geographic atrophy not involving the center of the macula.

   (c) AMD Category 4 participants with advanced AMD in one eye: 74 or more in the eye without advanced AMD.

   (d) AMD Category 4 participants without advanced AMD in either eye: 74 or more in one eye, 73 or less in the fellow eye:

   The visual acuity < 74 letters must be (1) consistent with AMD and (2) not considered more likely to be due to some other eye disease or condition (e.g., optic atrophy, retinal vascular occlusion, cataract). Both the presence of AMD lesions consistent with decreased visual acuity and the absence of another retinal or lens lesion considered to be a more likely cause of reduced visual acuity will be confirmed by the Reading Center evaluation of lens and fundus photographs.

2. Media clarity

   (a) For participants in AMD Categories 1 and 2, the Reading Center, based on evaluation of lens and stereo color fundus photographs, must find the media of both eyes to be sufficiently clear to discern potential small (< 63 microns in diameter) punctate or hard drusen located within a 2 disc diameter radius of the center of the macula.

   (b) For participants in AMD Category 3 or 4, the media must be clear enough to allow photographic assessment of the characteristics of large drusen and discernment of subtle abnormalities of more advanced AMD in their early stages. However, for eyes with advanced AMD, the media need only be clear enough to allow recognition of advanced AMD.

3. Pupillary dilation $\geq$5 mm in each eye for all participants, except that dilation <5 mm in an aphakic eye will not exclude a Category 3 or 4 participant with adequate quality fundus photographs.

3.1.3.2 Ocular exclusion criteria.

A. Persons not meeting criteria for AMD category 1, 2, 3 or 4 are ineligible.

B. Persons with any of the following characteristics in *each* eye are ineligible:

1. A visual acuity score of 73 or less.

2. Previous laser photocoagulation for AMD or peripapillary CNV.

3. Aphakia and no evidence of at least one large drusen (> 125 microns in diameter) or extensive intermediate drusen, or definite noncentral geographic atrophy, or advanced AMD (Section 3.1.2.5).

4. Evidence of advanced AMD.

C. Persons with any of the following characteristics in *either* eye, are ineligible:

1. The presence of diabetic retinopathy in a person with diabetes mellitus, unless the retinopathy is limited to fewer than 10 microaneurysms and/or small retinal hemorrhages.

2. Angioid streaks.

D. AMD Category 1 or 2: Persons with any of characteristics 1 through 6 (listed below) in *either* eye are ineligible.

AMD Category 3 or 4: Persons with any of characteristics 1 through 6 (listed below) in *either* eye are ineligible, with the following exception:

If one of these characteristics is present in one eye, and the examining ophthalmologist and Reading Center concur that it is uniocular, the participant is eligible for:

a) Category 3 if the fellow eye has one or more large drusen, or has extensive intermediate drusen, or has definite geographic atrophy not involving the center of the macula, or
b) Category 4 if the involved eye has advanced AMD.

1. Media not sufficiently clear to obtain fundus photographs meeting ocular eligibility criterion 2, media clarity, above.

2. Any of the following ocular diseases or conditions, the presence of which may now or in the future complicate evaluation of the progression of cataract or AMD:

(a) Central serous choroidopathy

(b) Optic atrophy

(c) Surface wrinkling retinopathy (epiretinal membrane) that is more severe than the mild surface wrinkling retinopathy seen in example photographs 68 through 71

(d) Pigmentary abnormalities considered by the Clinical Center ophthalmologist or the Reading Center to be less typical of AMD than of some other condition, such as pattern dystrophy or chronic central serous retinopathy

(e) Myopic crescent of the optic disc the width of which is $\geq$ 50 percent of the longest diameter of the disc, or pigmentary abnormalities in the posterior pole considered by the clinic ophthalmologist or the Reading Center more likely to be due to myopia than to AMD (for example, because of the presence of few or no drusen).

(f) Macular hole or pseudohole

(g) Retinal vein occlusion, active uveitis, presumed ocular histoplasmosis syndrome, other sight-threatening retinopathies, and other retinal degenerations

(h) Choroidal nevus within 2 DD of the center of the macula if it has areas of depigmentation and/or more than occasional small drusen related to it. Drusen over or adjacent to the nevus that appear by their size and distribution to be unrelated to the nevus will not exclude a participant.

(i) Other ocular diseases or conditions, the presence of which may now or in the future complicate evaluation of cataract or AMD.

3. Previous retinal or other ocular surgical procedures, the effects of which may now or in the future complicate assessment of the progression of cataract or AMD. Examples are argon laser trabeculoplasty, radial keratotomy, trabeculectomy, cryosurgery (except to repair a peripheral retinal hole), lamellar keratoplasty, pterygium surgery that affects or threatens the visual axis, radiation for ocular tumor, or repair of corneal or scleral laceration. Cataract surgery more than 6 months prior to randomization is not an exclusion criterion unless complicated by a condition that is causing or is likely to cause a decrease in visual acuity.

4. Current use of or likely need for systemic or ocular medications known to be toxic to the lens, retina, or optic nerve, such as:

(a) Deferoxamine

(b) Chloroquine/Hydrochloroquine (Plaquinil)

(c) Tamoxifen

(d) Chlorpromazine

(e) Phenothiazines

(f) Ocular or systemic steroids, unless participant is bilaterally aphakic or use of steroid-containing inhalers or nasal sprays is limited to less then 6 days a month on average. Any regular use of pills containing steroids, regardless of amount, excludes a participant.

(g) Ethambutol.

5. If the intraocular pressure is ≥26 mm Hg, or there is some reason to believe that the participant may have glaucoma (e.g., history of the diagnosis of glaucoma, past or present use of medications to control intraocular pressure, or disc/nerve fiber layer defects suggestive of glaucoma), then the absence of a glaucomatous visual field defect must be documented by a normal Goldmann, Humphrey, or Octapus perimetry test within 6 months prior to qualification. A copy of the field test must be maintained in the participant's AREDS record.

6. Cataract surgery within 6 months or capsulotomy within 6 weeks prior to the Qualifying Visit.

3.1.3.3 General eligibility criteria. Participants must meet each of the following general eligibility criteria for Phase II.

1. Randomized within 4 months following the Qualifying Visit (Chapter 6).

2. Age criteria:

a. AMD Category 1 and 2 participants: Age 60 through 80 years at the Qualifying Visit.

b. AMD Category 3 or 4 participants: Age 55 through 80 years at the Qualifying Visit.

c. Participants 78 years of age at the time of Phase I registration are eligible regardless of age at the Qualifying Visit.

3. Willingness to stop taking any supplements containing vitamin C, vitamin E, beta-carotene, zinc, or copper, other than those supplied by AREDS.

Willingness to stop taking other supplements is demonstrated by refraining from use of vitamin or mineral supplements other than AREDS-supplied Centrum® during the entire run-in period. Continued taking of nutritional supplements that are not part of the randomized trial (e.g., calcium) does not exclude a participant, provided that these supplements are taken 1 to 2 hours before or after the AREDS supplements.

4. Participants must have demonstrated that they have taken at least 75 percent of their run-in medication, as determined by an estimated count of the remaining Trial Medication tablets (exceptions may be made by appeal) and have indicated that they are willing to take the AREDS Study Medication for the next 7 years.

5. Likely to be available, willing, and able to undergo examinations at 6-month intervals for at least 7 years.

6. Informed consent. Each person to be enrolled must sign two informed consent forms. The first describes the responsibilities of the participant and the study during the run-in period. The second describes responsibilities following randomization. Model informed consent forms are given in Appendix B. Chapter 13 details the procedures for orienting a participant and obtaining his or her consent. A Phase II AREDS consent form must be signed even if a Phase I consent form was signed previously.

3.1.3.4 General exclusion criteria. Meeting any of the following criteria renders the participant ineligible for AREDS.

1. Unwilling or unable to stop taking supplements containing vitamin C, E, beta-carotene, or zinc other than AREDS-supplied Centrum® during the run-in period and for the next 7 years, or failure to take at least 75 percent of run-in medication as determined by an estimated count of Trial Medication tablets (exceptions may be made by appeal).

2. History of cancer with a poor 7-year survival prognosis.

3. Major cardiovascular or cerebrovascular event. Examples include severe myocardial infarction, cerebrovascular accident, and congestive heart failure. If the vascular condition appears stable and the initial event occurred more than 12 months ago, the participant is eligible if the study ophthalmologist believes the 7-year prognosis is good.

4. Hemochromatosis, Wilson's Disease, or history of oxalate kidney stones.

5. Chronic alcoholism or drug abuse.

6. Personality disorder or use of major tranquilizers (e.g., Haldol, Phenothiazine), indicating potential difficulty in long-term followup or adherence.

7. Current participation in other studies which are time-consuming and likely to affect adherence with the AREDS followup schedule.

3.1.3.5 Reading Center determinations of eligibility. The Reading Center will (1) review lens and fundus photographs for photographic quality and fundus photographs for the presence of disqualifying conditions, and (2) grade fundus photographs for the presence and type of age-related macular changes. If the quality of the lens or fundus photographs is unsatisfactory because of photographic techniques, retakes may be indicated; if the quality of fundus photographs remains unsatisfactory after retakes, the participant is ineligible (Section 3.1.3.1).

3.1.3.6 Recruitment requirements and goals. The AMD classification (Section 3.1.2) based on the determination of morphology by the Reading Center and the measurement of visual acuity by the Clinical Center will be used for determining eligibility. Each of the 10 funded Clinical Centers is expected to enroll 100 participants from AMD Category 1, 100 from Category 2, and 260 from Categories 3 and 4. The goal is to enroll 130 participants each in Categories 3 and 4. Centers should attempt to enroll 40 to 60 percent of the participants in each AMD category between the ages of 60 to 67 years. No more than 60 percent of the participants in Category 1 or Category 2 may be less than 68 years of age in any clinic. In addition, the study had a goal of enrolling participants of black race such that this cohort would comprise 4% of the AREDS study population.

3.1.4 Methods

3.1.4.1 Study population. At least 4,600 participants meeting the eligibility criteria set forth in Section 3.1.3 will be enrolled in AREDS (the enrollment procedure is described in Chapter 6). Of these, an expected 100 bilaterally aphakic participants will be excluded from the cataract studies. Of the 4,500 participants included in the cataract study, 3,500 are expected to be free of lens opacity or have lens opacity insufficient to affect fundus photographs at the time of randomization, and 1,000 will have more advanced opacity (Exhibit 3-4). For the AMD studies, in which all 4,600 participants will take part, 1,000 are expected to be enrolled in AMD Category 1, 1,000 in Category 2, and 2,600 in Categories 3 and 4, if the Clinical Centers meet the recruitment requirements (Section 3.1.3.6). A goal is to enroll 1,300 participants each in Categories 3 and 4 (Exhibit 3-4).

3.1.4.2 Risk factors. Participants will be classified according to the presence of various potential risk factors (characteristics) (Exhibits 3-10 and 3-11) from information collected in the baseline interview and from the lens and fundus photographs.

3.1.4.3 Clinical trial. Participants will be enrolled in AREDS after examination during the Qualifying Visit and successful completion of a run-in period lasting at least 1 month during which they will be asked to take placebo tablets (Trial Medication). At the time of enrollment at the Randomization Visit (Chapter 6), the Coordinating Center will randomly assign the participants to daily treatment with antioxidants, zinc, antioxidants and zinc, or placebo (Study Medication) (Exhibit 3-2). The toxicity of the treatments will be monitored through interview and laboratory tests. Laboratory tests for toxicity monitoring will consist of baseline and annual hematocrit tests of all enrolled participants and lipoproteins tests [high density lipoprotein (HDL) and low density lipoprotein (LDL)] on all participants from three Clinical Centers (Devers Eye Institute, Johns Hopkins Universities, and the NEI Clinical Center). Adherence will be assessed by estimated tablet counts on all participants and serum zinc and antioxidant levels for participants from Devers, Hopkins, and NEI. Details on the run-in period and the formulation and toxicity of the treatments

are provided in Chapter 10. Both participants and clinic personnel will be masked with regard to the treatment assignment.

3.1.4.4 Followup schedule. All participants randomized will be followed during the clinical trial by clinic examination at 6-month intervals for a minimum of 5 years. Following the clinical trial participants will be followed by clinic exam annually. The important features of each examination are provided in Chapter 6 for the clinical trial and Chapter 19 for the study of clinical course extension.

3.1.4.5 Study outcome variables. Morphologic and visual acuity changes are both important outcomes in the studies of clinical course and the clinical trials of cataract and AMD. However, it may often be difficult to determine the degree to which cataract, AMD, or other abnormalities are contributing to any visual decrease observed. Although the exclusion of persons with sight-threatening diseases makes the occurrence of visual impairment from causes other than cataract and macular degeneration unlikely during early followup, such impairments will become more frequent as followup progresses. Morphologic changes have the advantage of being disease-specific and photographically verifiable in a masked examination. A major disadvantage is their uncertain association with functional disability. The impact of these morphologic changes on visual function will be measured primarily by an accompanying doubling of the visual angle (15 letter decrease in visual acuity compared to Randomization Visit score). Participants will be assessed photographically at baseline, at two years, and annually thereafter for the progression of lens opacities and macular degeneration. A sequential sample of participants graded by the Reading Center as having any PSC opacity in the Qualifying Visit photographs will have lens photographs (Neitz, slit lamp, and red reflex) taken at the first Annual Visit. Any PSC opacity is defined as involvement of at least 1% in any subfield of the standard lens area (5 mm diameter circle), resulting in involvement of at least 0.1% in the standard area. This sample will provide an estimate of expected PSC events between the baseline photographs and the 2-year photographs.

Other outcome variables that will be assessed as part of the clinical trials will include cardiovascular events, cancer, morbidity, and mortality from all causes and, possibly, from specific causes.

Photographs. Photographs will be used in the cataract and AMD studies of clinical course and prognosis, risk factors, and clinical trials to assess participant outcome. Baseline, two-year, and subsequent annual lens photographs are required for all phakic eyes of AREDS participants (Chapters 6 and 8). Lens photographs are required at the first Annual Visit in a sample of participants with any PSC opacity present on Qualifying Visit photographs. Lens photographs at the first Annual Visit are required for all participants whose visual acuity has dropped by 10 or more letters compared to the Randomization Visit score (event photo; Section 3.1.2.9). Lens photographs will be classified by the Reading Center according to the AREDS Lens Opacity Grading System (Section 3.1.2.1).

Baseline, two-year, and thereafter annual fundus photographs are required for all eyes of AREDS participants (Chapters 6 and 8). Fundus photographs are required at the first Annual Visit if the participant's visual acuity has dropped by 10 or more letters compared to the Randomization Visit score. The Reading Center will grade the severity of fundus abnormalities and classify fundus

photographs according to the four AMD categories and according to the 11-step AMD Severity Scale (Section 3.2.2.3).

In addition, event photographs (Section 3.1.2.9) to document fundus and lens status are required at Nonannual Visits if visual acuity has dropped for the first time by 10 or more letters as compared to the visual acuity score determined at the Randomization Visit.

Visual acuity. Best-corrected visual acuity will be measured by the method outlined in Chapter 7 (a modification of the method used in the Early Treatment of Diabetic Retinopathy Study [ETDRS]), at the Randomization Visit, at Annual Visits, and at any other time lens or fundus photographs are taken. Visual acuity will be measured with Chart R at the Qualifying Visit and at Nonannual Visits. If the visual acuity measured at a Nonannual Visit has dropped by 10 or more letters compared to the Randomization Visit score for the first time, visual acuity will be measured as described in Chapter 7. If visual loss (decrease from the Randomization Visit by 10 letters or more) for the first time is present, the examining ophthalmologist will be asked to specify the most likely causes of the loss. The most likely cause of visual loss must be specified on the Annual Visit form every time a drop in visual acuity by 10 letters or more from the Randomization Visit is observed.

3.1.5 Statistical Considerations

3.1.5.1 Units of analysis. Although AREDS will study both eyes of all participants, the primary unit of data analysis and the unit of randomization in the clinical trial will be the participant. In the study of clinical course and prognosis, the unit of analysis may be either the participant or the eye, depending on the analysis. When paired eyes are included in an analysis involving statistical inference, it is necessary to take into account the likely positive correlation between the eyes with respect to the variable studied.[1,2] Although sophisticated methods for dealing with this problem are available,[3-9] some of which are based on mathematical models that involve assumptions, simple methods involving no assumptions can also be used. For example, the analysis can be limited to a single eye per participant, such as analysis of either "better" or "worse" eyes, or the information from paired eyes can be combined by classifying participants according to whether both eyes, one eye, or no eyes sustained a specified event (e.g., visual function loss).

3.1.5.2 Power considerations. Power considerations, although discussed in subsequent sections of this chapter for both morphologic and visual acuity outcomes, are driven by morphologic outcomes. Power assessments for visual acuity loss are problematic because the data needed on visual acuity loss are lacking and because it is difficult to ascribe visual acuity loss to a specific cause in the presence of competing causes. The majority of AREDS participants will have at least 7 years of followup. The power considerations presented in this chapter are based on 7-year incidence rates.

3.1.5.3 Multiple tests of hypotheses. An important issue to be considered in AREDS is the size of the alpha (α) error given the multiple tests of hypotheses that will be carried out because of multiple outcome variables, multiple interventions, multiple risk factors, and multiple subgroup analyses. Although multiple statistical tests will be performed in both the study of clinical course and prognosis and in the clinical trial, they are likely to be more abundant in the former because it

is largely a hypothesis-seeking study, whereas the latter is focused more on hypothesis testing. How to adjust α for multiple testing, whether such adjustment is needed, and whether Bayesian methods avoid the need for adjustment are topics of controversy in the scientific literature.[10,11] In AREDS it will be desirable to consider this issue separately for (a) the study of clinical course and prognosis and (b) the clinical trial.

3.1.5.4 Toxicity monitoring. Interim analyses will be performed to evaluate the efficacy and toxicity of the nutrient supplements. Little is known about the toxicity associated with long-term use of nutritional supplements. Information on blood tests (Chapter 18) will be monitored at baseline and during followup, when morbidity and mortality will also be evaluated. Although numerous methods are available for stopping interventions early when benefit or harm is demonstrated, such methods typically assume only a single outcome.[12-15] A rigid stopping rule is not practical in AREDS because of the multiplicity of outcomes. The statisticians at the Coordinating Center will work closely with the DSMC to evaluate the strength of the evidence for or against continuing the clinical trial. Supporting evidence will be sought from subgroup analyses and from results of other studies. A statistical procedure has been developed for sequential monitoring of multiple outcomes to serve as one of the guidelines for early termination of the study.

3.1.5.5 Interim Analysis for Safety and Efficacy. For the purpose of sequential monitoring, the three primary endpoints are: 1) progression to advanced AMD in at least one eye, 2) progression of lens opacity of any type or the occurrence of cataract surgery in at least one eye, and 3) decrease by 15 letters in visual acuity score in at least one eye. An eye progresses to advanced AMD with the development of one or more of the following: geographic atrophy involving the center of the macula, retinal pigment epithelial (RPE) detachment, serous detachment of the sensory retina, subretinal hemorrhage, disciform scar, scar of previous photcoagulation for treatment of CNV. Progression of nuclear, cortical, and PSC opacities is defined as follows:

Nuclear:	1.5 unit increase from baseline measure
Cortical:	10% increase in area from baseline within the standard 5mm circle
PSC:	5% increase in area from baseline within the standard 5mm circle

A group sequential procedure for a single time to event outcome variable is described by Lan and Lachin[16]. Their procedure is based on the alpha spending function approach of Lan and DeMets[17]. The alpha level or Type I error in a non-sequential design is assigned to one (final) analysis. In repeated interim analyses the cumulative Type I error increases with each interim evaluation. The goal of a group sequential design is to control the overall Type I error rate. Here, overall means accounting for interim analyses. The alpha spending function approach gives a rule for allocating some of the prespecified Type I error to each interim analysis. This rule depends on the fraction of the total "information" of the trial accumulated by the time of interim analysis. When the logrank test is used to compare the survival pattern of two treatment groups, the fraction of information at an interim analysis is the fraction of the total number of events to be accrued in the entire trial. In AREDS the total number of events to be accrued is not known. Lan and Lachin[16] suggest estimating information in terms of patient exposure time (exposure time is the time from randomization to end of follow-up or until an event is observed). Based on the spending function defined in terms of estimated information time, they describe the method for computation of the logrank test group

sequential boundaries. Even though the estimated information fraction is used to determine the amount of overall Type I error allocated to a particular interim analysis, the actual number of events observed is used to compute the boundary.

AREDS has adopted a group sequential procedure by extending the Lan and Lachin[16] approach to a study with multiple time to event outcome variables. The overall Type I error rate is controlled at a prespecified level, accounting for both multiple endpoints and interim analyses. First, Bonferroni adjustment is used to distribute the (sometimes called experiment-wise) Type I error alpha among multiple endpoints. For example, if $\alpha = 0.05$ is assigned to the group of statistical tests of five endpoints, then $\alpha_5 = \alpha/5 = 0.01$ would be used to compute the boundary for each endpoint. The spending of the fraction of overall Type I error allocated to each outcome (α_5) through interim analyses is then controlled by the alpha spending function for that endpoint as mentioned above.

In the clinical trial of AMD and cataract, the AMD events and cataract events are independent, but the visual acuity events are potentially correlated with AMD and cataract events. The Bonferroni approach to account for testing of multiple endpoints is valid whether or not the endpoints are correlated. For the purposes of stopping guidelines for treatment efficacy, assuming no interaction, the factorial design will be ignored and analyses of antioxidants vs. no antioxidants and zinc vs. no zinc will be considered, adjusting alpha levels accordingly for each analysis. Therefore, the five comparisons to be made at each interim analysis are:

- Progression to advanced AMD between antioxidants and no antioxidants groups
- Progression to advanced AMD between zinc and no zinc groups
- 15 letters drop in VA score between antioxidants and no antioxidants groups
- 15 letters drop in VA score between zinc and no zinc groups
- Progression of lens opacity of any type between antioxidants and no antioxidants groups.

As the long term effects of nutritional supplements are not clearly understood, the study should be stopped early only if there is strong evidence of benefit or harm. The symmetric O'Brien-Fleming[15] boundary is appropriate for AREDS as it is very conservative (requires a large treatment effect to signal stopping) during the early analyses. The spending function which approximates the O'Brien-Fleming boundary will be used to monitor the efficacy of nutritional supplements.

The estimated information fraction, as defined in Lan and Lachin[16], is the ratio of total exposure time up to the time of interim analysis and total exposure time by the end of the study. The true exposure time of the participants who have not experienced an event by the time of interim analysis is not known. For these subjects the exposure time is defined as the time from randomization to last followup. The total exposure until the end of study is calculated as the time from randomization to April 15, 2001. This estimated information fraction could be different for the three end points, because participants may experience each event at different times.

The amount of overall alpha (α) allocated to each comparison is $\alpha_5 = \alpha/5$. For each of the five comparisons, the amount of α_5 available for interim analysis performed at time *t* is $\alpha_5(t)$, where $\alpha_5(t)$ is obtained from the O'Brien-Fleming type spending function based on estimated information time. The symmetric boundary for each comparison will be computed using the software of Reboussin et al[18]. For purposes of illustration, Table I gives the critical values for the test statistic computed at some arbitrary information time points with overall alpha level fixed at $\alpha = 0.05$ and thus $\alpha_5 = 0.01$. In the application of this procedure, the true boundary to be computed at each time of analysis will be based on the actual number of events up to that time.

The alpha spending function approach will also be applied to sequential monitoring of mortality. Because mortality is not a study endpoint, but rather an adverse event, it will not be included among the multiple comparisons of endpoints. Considerations of multiple comparisons will apply only to three tests of mortality from the factorial design, to be made at each interim analysis:

- Zinc vs. placebo
- Antioxidants vs. placebo
- Antioxidants+zinc vs. placebo

Special interest in, and responsibility for, safety led the DSMC to select an overall alpha of 0.10 and a one-sided procedure in data monitoring that ignores any possible beneficial effects on mortality. In addition, the DSMC also selected a Pocock[19] type spending function for sequential monitoring, which results in early stopping under less extreme conditions than would the O'Brien-Fleming boundaries.

The choice to evaluate each formulation against placebo instead of using the classic main effects test of a factorial design was made because neither cataract nor AMD are considered life-threatening conditions, and therapeutic strategies for these conditions must be carefully evaluated for deleterious systemic effects. If a specific formulation is harmful, a monitoring guideline must be sensitive to alert the monitoring committee of potential harm early in the trial. Factorial designs in a clinical trial setting are typically underpowered to detect interactions that may be clinically relevant. A guideline for mortality which tests for main effects in the absence of a statistically significant interaction effect, although methodologically correct, may mask the effects of a harmful formulation. On the other hand, testing individual formulations in a factorial design increases the potential for declaring differences when in fact no difference exists (Type I error). For this reason the monitoring plan is considered a guideline, which offers some protection against Type I error ($\alpha = .10$), and which must consider the consistency of all data including the main effects analyses.

Table II gives the critical values for the test statistic computed at the information times given in Table I. The amount of alpha allocated to each comparison is 1/3 of alpha, or $\alpha_3 = 0.033$. In the application of this procedure, the true boundary will be computed at each time of analysis, based on the actual number of deaths up to that time.

Table I: Examples of Critical Values of the Test Statistic Computed for either AMD or Visual Acuity Comparisons (Zinc vs. No Zinc, Antioxidants vs. No Antioxidants), and Cataract (Antioxidants vs. No Antioxidants).

Information Fraction	Lower Bound	Upper Bound	Cumulative Exit Prob.	
			MC Adj.	No Adj.*
0.35	-4.60	4.60	0.00000	0.00030
0.50	-3.80	3.80	0.00014	0.00305
0.65	-3.31	3.31	0.00100	0.01087
0.80	-2.96	2.96	0.00340	0.02442
0.90	-2.80	2.80	0.00618	0.03629
1.00	-2.65	2.65	0.01000	0.05000

* Under "No Adjustment for Multiple Comparisons", these cumulative exit probabilities correspond to upper and lower bounds (not shown) computed from the alpha=0.05 spending function.

Table II: Examples of Critical Values of the Test Statistics for Mortality Comparisons (Zinc Vs. Placebo, Antioxidants Vs. Placebo, Zinc+Antioxidants Vs. Placebo)

Information Fraction	Lower Bound	Upper Bound	Cumulative Exit Prob.
0.30	-8.0	2.21	0.01372
0.40	-8.0	2.38	0.01726
0.50	-8.0	2.39	0.02046
0.60	-8.0	2.38	0.02338
0.80	-8.0	2.29	0.02854
1.00	-8.0	2.27	0.03300

3.1.5.6 Interim Analyses for Secondary Outcomes. AREDS has adopted a group sequential procedure to perform interim analysis for testing efficacy using the primary endpoints. At future interim looks at the data, treatment efficacy will also be evaluated by performing several secondary analyses. Early stopping based on these secondary analyses alone is unlikely. However, because of interim looks at the data, monitoring guidelines for these secondary analyses will be used to preserve alpha (Type I error) for the final data analysis. We propose a simple, but flexible procedure which controls the experimentwise Type I error for the secondary analyses at a pre-specified level. The procedure allows for the number of secondary analyses within a treatment comparison to change over time.

The following secondary outcomes are specified in the Manual of Operations. More can be added without affecting the strategy.

AMD: (Cox model with both eyes included)

1) Geographic Atrophy (center)
2) Neovascular AMD development
3) Any drusen development (for those with no drusen at baseline)
4) Any large drusen development
5) Any pigment abnormality development

Visual Acuity:

1) Time to 10 letter drop using the Cox model with both eyes included. (Longitudinal analysis of average change in VA using GEE will also be performed to validate the results obtained using the Cox model.)

Lens Events: (Cox model with both eyes included)

1) Time to cataract surgery
2) Time to nuclear event
3) Time to cortical event
4) Time to PSC event (GEE models using longitudinal nuclear, cortical, and PSC scores (per patient) will also be developed).

The monitoring guidelines are constructed as follows:

Step 1: Choose the overall significance level for each treatment comparison; $\alpha(c) = 0.01$ (See Table III).

Step 2: Allocate a fraction of the overall alpha ($\alpha(c)$) for each time point; $\alpha_t(c) = 0.0001$ for the interim looks and $\alpha_t(c) = 0.0098$ for the final look.

Step 3: Compute the significance level (p-value) associated with the treatment comparison in each of the secondary analyses.

Step 4: Apply Hochberg's procedure for multiple comparison to assess the significance of these p-values (See Table IV).

Table III: Distribution of Type I Error.

Treatment Comparison	Year 99	Year 00	Final Analysis	Total α (for each comparison)
AX vs No AX	0.0001	0.0001	0.0098	0.01
Zn vs No Zn	0.0001	0.0001	0.0098	0.01
AX vs Placebo	0.0001	0.0001	0.0098	0.01
Zn vs Placebo	0.0001	0.0001	0.0098	0.01
AX+Zn vs Placebo	0.0001	0.0001	0.0098	0.01
Total α (at each time point)	0.0005	0.0005	0.0490	0.05

Hochberg's Procedure for Multiple Comparison: The Type I error allocated to a treatment comparison will be controlled for multiple analyses performed at each time point using the Hochberg's procedure described below.

1) Perform the relevant test of significance for each analysis and derive the corresponding
   p-values, $p_1, p_2, \quad ,p_N$.

2) Rank the p-values from largest to the smallest
   $p_{(N)} \geq p_{(N-1)} \geq \quad \geq p_{(2)} \geq p_{(1)}$

3) Compare the ranked p-values against the following α-levels

p-value	α-level
$p_{(N)}$	α
$p_{(N-1)}$	α/2
$p_{(N-2)}$	α/3
⋮	⋮
$p_{(2)}$	α/(N-1)
$p_{(1)}$	α/N

4) Start with the largest p-value, $p_{(N)}$, and compare it against the critical value α. If $p_{(N)} \leq \alpha$, then we can stop and declare the entire set of comparisons significant.

5) Otherwise, we proceed to the next largest p-value, $p_{(N-1)}$, and compare it to α/2. If $p_{(N-1)} \leq \alpha/2$, then we stop and declare that this difference and all those with smaller p-values are statistically significant. And so on.

Table IV: Critical α-levels for 10 Secondary Analyses.

Comparison	Ranked p-value	α-level
1	$p_{(10)}$	0.0001000
2	$p_{(9)}$	0.0000500
3	$p_{(8)}$	0.0000333
4	$p_{(7)}$	0.0000250
5	$p_{(6)}$	0.0000200
6	$p_{(5)}$	0.0000167
7	$p_{(4)}$	0.0000143
8	$p_{(3)}$	0.0000125
9	$p_{(2)}$	0.0000111
10	$p_{(1)}$	0.0000100

Thus, the smallest p-value will have to be less than 0.00001 to be considered significant at an interim look.

3.1.5.7 Analytic methods. AREDS is a longitudinal study with multiple outcome variables. When only one followup time is being considered, the simple T-test and its nonparametric analogue, the Wilcoxon-Mann-Whitney test will be used. Using analysis of covariance, these simple two-sample tests will be generalized to incorporate baseline values and covariates. The stochastic ordering test described by Wei and Lachin,[20] which allows for randomly missing data, is a natural multivariate analogue of the two-sample Wilcoxon-Mann-Whitney test and will be used to evaluate the repeated measures that will be taken at multiple time points.

Visual acuity outcomes (e.g., loss of 15 or more letters, occurrence of decrease in total visual acuity score to $\leq$ 35 letters) and morphologic endpoints (e.g., progression to advanced AMD, progression of lens opacity) will be analyzed in terms of one or more "events" using multivariate logistic regression. Time-dependent event rates will be analyzed by the life-table method. From life-table results, time-dependent event rates will be portrayed graphically. Estimates of event rates will include confidence intervals, and treatment effects will be tested with the log-rank method. Standard contingency table methods will also be used to evaluate disproportionate event rates on treatment arms following a prespecified followup interval. Consideration will be given to estimating missing visual acuity values by interpolation, as was done in the Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study.[21] Adjustments for missing observations by the methods of Choi and Stablein will also be considered.[22]

An alternative method of analyzing visual acuity will also be considered: the average number of letters lost. Although this method has the advantage of using the information from the entire visual acuity scale, rather than dichotomizing that scale (as in defining events), it cannot generally incorporate all the available followup information in a single, unified analysis; as a result, data on recently enrolled participants is often too sparse for analysis. Methods that will be considered for this type of analysis are described below.

When many time points are included, the repeated measures analysis does not yield a parsimonious summary of the data, even when the covariance assumptions are met. A mixed-effect model for longitudinal data analyses can provide an appropriate structure for analysis. For the i^{th} subject, the n_i x 1 response vector Y_i can be modeled as

$$Y_i = X_i \beta + r_i,$$

where X_i is an n_i x p design matrix of treatment and covariate effects for the i^{th} subject, β is the p-dimensional vector of parameters to be estimated, and r_i is the n_i x 1 vector of residuals. Unbalanced designs are explicitly permitted through X_i, and the model is particularly simple if, say, a linear deterioration in acuity occurs in all treatment groups.

The residual deviation from the mean, r_i, is typically modeled via the r_i x q matrix Z_i as

$$r_i = Z_i b_i + e_i,$$

where $Z_i b_i$ describes the deviation of the i^{th} subject mean from the mean for all subjects and e_i represents residual within subject variation. Taking $E(r_i) = 0$, the major challenge is specifying the form of the var $(r_i) = \Sigma_i$. If Σ_i is known, ordinary least squares apply. Both generalized least squares and restricted maximum likelihood methods can be used in practical applications where Σ_i is unknown. The analysis of visual acuity data using the mixed-effects model will be implemented using the software developed by the SAS Institute Inc.

The generalized estimating equations approach (GEE), proposed by Liang and Zeger, provides an alternative method for analyzing longitudinal data. It models[23] the marginal expectation of the outcome variable as a function of covariates while accounting for correlation among the repeated observations for a given cluster (with only one class). The variance is assumed to be a known function of the mean. Starting from a "working" correlation matrix for the observations for each cluster, the GEE approach gives consistent estimates of regression coefficients and their variances. Assuming the data are missing at random, these estimates are robust to mis-specification of the "working" correlation matrix. This approach is appropriate when the goal is to obtain the regression equation for the marginal expectation when the correlation is a nuisance.

The GEE method described above will be used to analyze the longitudinal visual acuity data obtained from one eye per subject (left, right, or the average number of letters lost) using the SAS® procedure GENMOD. When data from both eyes are to be used simultaneously in the analysis, the method based on second-order generalized estimating equations (GEE2) is most appropriate. This method is an extension of GEE to handle correlation between multiple classes within a cluster[24]. At present, the software developed for implementation of GEE2 is limited to binary outcome variables.

For analyses of data from both eyes, Cox's proportional hazard model for multivariate time to event data developed by Wei, Lin, and Weissfeld[25] and Lee, Wei, and Amato[26] will be used. Separate analyses will be performed for each of the three primary endpoints, that is, for visual acuity events (loss of 15 or more letters) and the two morphologic events, progression to advanced AMD and progression of lens opacity. This approach is similar to the generalized estimating equation's methodology of Liang and Zeger for analysis of longitudinal data. The marginal distribution of time to event for each eye is formulated with the Cox proportional hazard model. It is natural to assume common baseline hazard functions for the two events from the same person. As in the GEE approach, modeling of the correlation between the paired eyes is not of interest and will be treated as a nuisance. This approach yields consistent estimates of the regression parameters and robust variance-covariance matrix, leading to efficient estimation of treatment effect. Implementation of this approach will be carried out using one of the recently developed software packages such as COXPH (a function in S-PLUS 3.3 for Windows), MULCOX2 (Fortran), and SAS procedure PHREG. Simultaneous analysis of the three primary endpoints including data from both eyes will also be performed using this approach.

Although the incidence of morbidity associated with treatment is not expected to be great (Chapter 10), toxicity will be monitored by evaluating the blood specimens and treatment imbalances in reports of adverse experiences or morbidity (Chapter 7). Blood studies will be evaluated at baseline and at multiple followup time points. Standard statistical tests using normal theory will be readily applicable for assessing these laboratory data.

3.2 STUDY OF CLINICAL COURSE AND PROGNOSIS

The design of the AREDS study of clinical course and prognosis is described in Section 3.2.1 for cataract and Section 3.2.2 for AMD.

3.2.1 Cataract

The design of the study of the clinical course and prognosis of cataract is illustrated in Exhibit 3-5.

3.2.1.1 Objectives. The objectives of the study of the clinical course and prognosis of cataract is to answer the following four questions:

1. In eyes without lens opacity, what is the incidence rate of
   (a) Any lens opacity
   (b) Nuclear opacity
   (c) PSC
   (d) Cortical opacity?

2. In eyes with lens opacity, what is the rate of progression of
   (a) Any lens opacity
   (b) Nuclear opacity
   (c) PSC
   (d) Cortical opacity?

3. In eyes with lens opacity, what is the incidence rate of
   (a) Doubling of the visual angle and
   (b) Cataract surgery
      (1) For all eyes and
      (2) For eyes with specific types of opacity?

4. Can the existing severity scales for nuclear, cortical, and PSC lens opacities be refined?

3.2.1.2 Study population. All bilaterally and unilaterally phakic AREDS participants will comprise the study population (4,500 expected). Of these, 3,500 are expected to be bilaterally phakic without lens opacity affecting the fundus photographs in either eye and 1,000 are expected to be unilaterally phakic or with some lens opacity in at least one eye.

3.2.1.3 Outcome variables. The outcome variables are progression of cataract, cataract surgery, and visual acuity score.

Progression of cataract. The primary outcome for this study is the progression of a nuclear, cortical, or PSC opacity in at least one eye of a participant. The term "progression" encompasses both incidence and progression. Progression will be evaluated separately for any lens opacity and for each of the three types of opacities (cortical, nuclear, and PSC).

Lens status will be determined by a grading of the lens photographs by the Reading Center according to the AREDS Lens Opacity Grading System (Exhibit 3-3). Using this system, nuclear opacities will be graded on a decimalized scale using 7 photographic standards, and cortical and PSC opacities on a continuous scale. Progression of disease using the lens scales will be also evaluated by considering distributions of change between baseline and followup.

During the first 6 months of Phase II, the reliability of the lens grading system will be assessed and refinements will be made as needed by the Reading Center.

Cataract surgery. Cataract surgery will be an additional outcome variable (endpoint). A participant will reach the cataract endpoint after cataract surgery in at least one eye. As an outcome variable, cataract surgery will be classified into two types:

- Cataract surgery accompanied by documented progression
- Any cataract surgery.

Visual acuity. The primary visual acuity outcome is the first occurrence of a doubling of the visual angle (a 15-letter decrease in visual acuity score) judged by the examining physician to be a result of cataract.

Specific outcomes. Some of the specific outcome variables for the study of clinical course and progression of lens opacity are:

- Doubling of the visual angle (a decrease in the visual acuity score of 15 or more letters) attributable to (a) cataract and (b) all causes
- Photographic evidence of progression on the nuclear opacity scale (Exhibit 3-3)
- Photographic evidence of progression on the PSC opacity scale (Exhibit 3-3)
- Photographic evidence of progression on the cortical opacity scale (Exhibit 3-3)
- Photographic evidence of development of two or more of the three types of lens opacities (nuclear, cortical, PSC)
- Surgery for age-related cataract.

3.2.1.4 Statistical considerations.

Lens opacity. The incidence and progression rates of lens opacity will be calculated. The incidence of lens opacity is defined as the occurrence of opacity in either eye of a participant who had no opacity at baseline in either eye. Progression is defined as an increase in the grade of opacity in at least one eye of a participant who had some opacity at baseline. In addition, the incidence rates will be calculated for (a) the doubling of the visual angle in at least one eye when the visual loss is attributed to cataract and (b) cataract surgery for participants with and without lens opacities at baseline. Life-table methods will be used in these analyses.

Exhibit 3-6 gives the 95-percent confidence intervals for various incidence and progression rates in the expected 3,500 participants without lens opacity and the 1,000 with lens opacity without adjustment for dropouts. If treatment is effective, then the incidence rates for the treated and control groups will be calculated separately.

3.2.2 AMD

The design of the study of the clinical course and prognosis of AMD is illustrated in Exhibit 3-7.

3.2.2.1 Objectives. The objective of the study of the clinical course and prognosis of AMD is to answer the following four questions:

1. What is the incidence rate of advanced AMD in participants in
   (a) Category 1 (no drusen or nonextensive small drusen)
   (b) Category 2 (intermediate or extensive small drusen or pigment abnormalities)
   (c) Category 3 (extensive intermediate drusen, large drusen, or noncentral geographic atrophy),
   (d) Category 4 (one eye with advanced AMD regardless of visual acuity score, or one eye with a visual acuity score of 73 or less with the decrease attributable to AMD; and the fellow eye with no evidence of advanced AMD and a visual acuity score of 74 or more)?

2. What is the incidence rate of doubling of the visual angle in participants in
   (a) Category 1
   (b) Category 2
   (c) Category 3
   (d) Category 4?

3. In persons without large drusen, what is the rate of incidence and progression of AMD (e.g., incidence of drusen, incidence or progression of pigment abnormalities, and increase in the size or area of existing drusen)?

4. Can valid and reproducible severity scales for macular degeneration be developed?

3.2.2.2 Study population. All AREDS participants are eligible for the study of the clinical course and prognosis of AMD.

3.2.2.3 Outcome variables. The outcome variables are progression to advanced AMD, visual acuity score, and AMD severity score.

Progression to advanced AMD. The primary morphologic outcome is the incidence of advanced AMD (advanced AMD is defined in Section 3.1.2).

Visual acuity. The occurrence of doubling of the visual angle (a decrease of 15 or more letters from the Randomization Visit visual acuity score) attributable to progression of macular degeneration.

AMD severity score. An 11-step AMD Severity Scale has been developed for measuring AMD progression in AREDS (Exhibit 3-8), the validity and reliability of which will be evaluated by the Reading Center. If the scale is found to be valid and sufficiently reliable, disease progression will be defined by distributions of change between baseline and followup visits.

Specific outcomes. Some specific outcomes for the study of clinical course and prognosis of AMD are:

- Photographic evidence of development of advanced AMD
- Doubling of the visual angle (a decrease in the visual acuity score of 15 or more letters) attributable to (a) AMD and (b) all causes
- Photographic evidence of development of pigment abnormalities in participants without pigment abnormalities at baseline
- Photographic evidence of development of large drusen (> 125 microns) or of the more severe lesions of AMD in persons without large drusen at baseline
- Evaluation of the validity and reliability of the 11-step AMD Severity Scale (Exhibit 3-8).

3.2.2.4 Statistical considerations. Incidence rates will be calculated for (a) advanced AMD in at least one eye in participants in AMD Categories 1, 2, and 3 and in the eye without advanced AMD in participants in AMD Category 4, and (b) the doubling of the visual angle in at least one eye when visual loss is attributed to AMD.

Separate rates will be calculated for each AMD category. Life-table methods will be used in these analyses.

Exhibit 3-9 gives the 95-percent confidence intervals for various rates based on the expected 1,000 participants to be enrolled in each of AMD Categories 1 and 2 and the 1,300 to be enrolled in each of Categories 3 and 4 without adjustment for dropouts. If treatment is effective, then the incidence rates for the treated and control groups will be calculated separately.

3.3 RISK FACTOR STUDY

The design of the AREDS risk factor study is described in Section 3.3.1 for cataract and Section 3.3.2 for AMD.

3.3.1 Cataract

Possible risk factors (baseline characteristics) for the development and progression of the lens opacities to be studied are listed in Exhibit 3-10 along with the proportion of the study population expected to have each characteristic.

3.3.1.1 Objectives. The objective of the risk factor study for cataract is to answer the following five questions:

1. What are the risk factors for development and progression of lens opacities?

2. What are the risk factors for (a) doubling of the visual angle attributable to lens opacity and all causes and (b) cataract surgery?

3. Are the type and severity of lens opacity at baseline associated with (a) a risk of visual acuity loss and (b) incidence of cataract surgery?

4. Does the presence of age-related macular changes affect the prognosis for visual improvement after cataract surgery?

5. After controlling for age and other possible confounding variables, is the incidence or progression of lens opacity or cataract surgery independent of the stage of AMD?

3.3.1.2 Study population. The population for the study of risk factors of cataract is the same as the population for the study of clinical course and prognosis (Section 3.2.1.2).

3.3.1.3 Outcome variables. The outcome variables and their definitions for the cataract risk factor study are the same as those listed in Section 3.2.1.3.

3.3.1.4 Statistical considerations.

Lens opacity. The main outcome variables to be studied are: (1) the development of lens opacities in at least one eye of participants with no lens opacity in either eye; (2) the progression of existing opacities in at least one eye of participants with some opacity at baseline; (3) the doubling of the visual angle in at least one eye with visual loss attributable to (a) all causes and (b) cataract only; and (4) cataract surgery. Multivariate logistic regression and Cox's proportional hazards model will be used to assess the importance of the various risk factors both independently and jointly. Exhibit 3-10 provides the relative risks (risk of developing lens opacity in persons exposed to a risk factor relative to those unexposed) for which the indicated sample size provides 90-percent power (two-sided $\alpha = 0.01$), given three incidence rates (0.10, 0.20, and 0.30) which may be observed in the unexposed group; the sample sizes are adjusted for dropouts.

3.3.2 AMD

Possible risk factors (baseline characteristics) for the development and progression of AMD are listed in Exhibit 3-11, along with the proportion of the study population expected to have each characteristic.

3.3.2.1 Objectives. The objective of the risk factor study for AMD is to answer the following five questions:

1. What are the risk factors for doubling of the visual angle?

2. Are severity of drusen and severity of pigment abnormalities risk factors for visual loss?

3. What are the risk factors for development and progression of AMD, and are they different for the atrophic and neovascular forms of the disease?

4. Is the presence of large drusen or advanced AMD associated with certain personal baseline characteristics?

5. Does cataract surgery affect the rate of progression of AMD?

3.3.2.2 Study population. All AREDS participants are eligible for the study of risk factors of AMD.

3.3.2.3 Outcome variables. The outcome variables for the study of AMD risk factors are the same as those listed in Section 3.2.2.3.

3.3.2.4 Statistical considerations. The most important outcome variables to be studied are: (1) the development of advanced AMD in (a) at least one eye in participants in AMD Categories 1, 2, and 3 and (b) the eye without advanced AMD of participants in AMD Category 4, and (2) the doubling of the visual angle in at least one eye with vision loss attributable mainly to AMD. Risk factors for the development of advanced AMD will be evaluated for the whole population and for each AMD category. Multivariate logistic regression and Cox's proportional hazards model will be used to assess the significance of the various risk factors both independently and jointly. Exhibit 3-11 provides the relative risks (risk of developing advanced AMD in persons exposed to a risk factor relative to those unexposed) for which the indicated sample size provides 90-percent power (two-sided $\alpha = 0.01$), given three incidence rates (0.10, 0.20, and 0.30) which may be observed in the unexposed group; the sample sizes are adjusted for dropouts.

3.4 CLINICAL TRIAL

One of the major questions to be addressed by the Age-Related Eye Disease Study is whether vitamin or mineral intake is associated with the risk of cataract or macular degeneration. Several case control studies have shown an association of antioxidant use with a decreased risk of cataract. A small clinical trial suggests zinc may reduce the rate of progression of age-related macular degeneration. The Age-Related Eye Disease Study will investigate these possible associations with both observational and clinical trial methodology.

Observational studies of vitamin and mineral intake will be part of AREDS, but the conclusions based on these results are limited by the possibility of uncontrolled confounding. Previous case-control studies have found associations, but the risk reduction observed is in the order

of magnitude that could be explained by confounding. Vitamin users are likely to be different from nonvitamin users in many possible factors such as socio-economic status, adherence with medical regimens, etc. Some of these factors will be known and can possibly be adjusted for and some will be unknown. In a randomized clinical trial confounding is less of a problem because these confounding factors, both known and unknown, will likely be balanced in each arm of the clinical trial. For this reason the clinical trial will be part of AREDS.

Exhibit 3-12 shows the randomization scheme for the 4,600 AREDS participants taking part in the clinical trial of cataract, the clinical trial of AMD, or both trials. Participants taking multivitamins at the time of enrollment will be offered Centrum®, an RDA level vitamin and mineral supplement. Participants accepting the offer of Centrum® will be asked to take Centrum® instead of the multivitamins (with or without minerals) they are currently taking. The 1,000 participants without age-related macular changes (AMD Category 1) will be randomized with 50-percent probability to either antioxidants or placebo; the 3,600 participants with age-related macular changes (AMD Categories 2, 3, and 4) will be randomized with 25-percent probability to one of four treatments: placebo, antioxidants, zinc, or antioxidants and zinc. The clinical trial will be double-masked -- neither the participants nor the clinic personnel will know the treatment assignment. The placebo will be inactive; the formulation of the antioxidants and zinc supplements are provided in Chapter 10.

3.4.1 Cataract

The design of the clinical trial of cataract is illustrated in Exhibit 3-13. The 4,500 expected AREDS participants who are phakic in at least one eye will be randomized to treatment with or without antioxidants. Although some participants will receive zinc, the purpose of zinc in AREDS is to evaluate its effect on AMD. There is no information indicating that the ingestion of zinc will affect the lens.

3.4.1.1 Objectives. The objective of this study is to answer two important questions:

1. Do high-dose antioxidant supplements reduce the rate of development of
   (a) Any lens opacity
   (b) Nuclear opacity
   (c) Cortical opacity
   (d) PSC opacity?

2. Do high-dose antioxidant supplements reduce the rate of progression of
   (a) Any lens opacity
   (b) Nuclear opacity
   (c) Cortical opacity
   (d) PSC opacity?

3.4.1.2 Study population. Of the expected 4,500 phakic participants, approximately half will be randomly assigned to treatment without antioxidants and half to treatment with high-dose antioxidant supplements.

3.4.1.3 Outcome variables. The primary outcome variable in the clinical trial of cataract is the occurrence of any of the following in at least one eye of a participant:

(a) Development of a lens opacity
(b) Progression of an existing lens opacity
(c) Cataract surgery in an eye with documented lens opacity.

The development and progression of opacities are defined in Section 3.2.1.3. Two additional outcome variables are noted below.

Visual Acuity. A doubling of the visual angle (a decrease in the visual acuity score of 15 or more letters) consistent with a change in lens status.

Toxicity. Morbidity and mortality events reported to be possibly or definitely related to study supplements on the Adverse Experience Report (Appendix C) will be classified as toxic outcomes. Imbalances among treatment arms of reported morbidity and mortality regardless of relationship to the study supplements will also be reported.

3.4.1.4 Statistical considerations. For the clinical trial of cataract, there will be approximately 4,500 participants divided with equal probability into two study groups (antioxidants, no antioxidants). The effect of the antioxidants on the development and progression of cataract is the main analysis to be performed.

Dropout. An expected 4,500 phakic participants will be randomized to antioxidants or placebo as described in Section 3.4.1.2. Based on national age-specific mortality statistics and taking into account the age and sex of the participants and that, at the time of enrollment, they will be healthy and have a good prognosis for 7-year survival, the cumulative death rate over a seven-year period is estimated to be 14 percent. Another 5 percent can be expected to drop out, and some dropouts will experience progression and some deaths will occur before these individuals are lost to the study. Thus, it can be expected that 15 percent of the participants will be lost to followup prior to having an outcome, leaving 3,825 participants (2,975 with no opacity and 850 with opacity at baseline) with 7-year followup or an observed outcome prior to dropout.

Nonadherence. It is assumed that 30 percent of participants assigned to placebo will begin to supplement with an equivalent of the active treatment (drop-in) as follows: 2 percent in each of years 1 and 2, 4 percent in each of years 3 and 4, and 6 percent in each of years 5, 6, and 7.

It is assumed that 20 percent of participants assigned to active treatment will stop taking all treatment as follows: 2 percent in year 1, 1 percent in year 2, 2 percent in year 3, 3 percent in year 4, and 4 percent in each of years 5, 6, and 7.

Treatment effect. Estimates based on unpublished data from Framingham Eye Study II indicate that the 7-year incidence rate for cataract is about 50 percent for persons aged 60 to 75 years. Shown in Exhibit 3-14 are the expected number of events in the absence of a treatment effect based on the following assumptions. During the 7-year period, 40 percent of the participants with no lens opacity at baseline will develop a lens opacity, resulting in 1,190 events, and 5 percent will undergo cataract surgery, resulting in 150 events. (Morphologic progression will not necessarily be

documented for these events.) Among those who begin the study with some lens opacity, 80 percent will experience progression of lens opacity, resulting in 680 progression events, and 10 percent will have cataract surgery, resulting in 88 events.

Too few cataract surgery events are expected for adequate testing of a treatment effect. The primary outcome variable of the clinical trial is progression of lens opacity, as defined in Section 3.2.1.3. Based on the Framingham data, 50 percent of the phakic participants are expected to experience progression of opacity within 7 years. The study will test whether the use of high doses of antioxidants reduces this rate by at least 10 to 20 percent. Exhibit 3-15 summarizes the different event rates of participants receiving placebo and various levels of treatment effects for which the study has 90 percent power to detect. Exhibit 3-15 assumes the following:

- two-arm comparisons
- no interaction
- a 1-year lag of treatment effect
- 15 percent of participants are lost before experiencing an event (lost to followup or death)
- 30 percent of participants assigned to placebo will begin to supplement with an equivalent of the active treatment (drop-in) as follows: 2 percent in each of years 1 and 2, 4 percent in each of years 3 and 4, and 6 percent in each of years 5, 6, and 7.
- 20 percent of participants assigned to active treatment will stop taking all treatment as follows: 2 percent in year 1, 1 percent in year 2, 2 percent in year 3, 3 percent in year 4, and 4 percent in each of years 5, 6, and 7.
- one-sided $\alpha = .025$
- 90-percent power
- 60 percent of participants will choose to take Centrum® (AREDS-supplied vitamins and minerals) at randomization.

Approximately 4,500 participants will initially be available for analysis for the cataract outcome. Assuming 15 percent are lost prior to experiencing an event, a total of 3,825 participants will be available for observation at 7 years or will have experienced an event prior to loss; 2,295 of which will have chosen to take vitamins at randomization and 1,530 will not. Approximately 50 percent of participants assigned to placebo are expected to experience progression of lens opacity. Exhibit 3-15 illustrates that the study has at least 90 percent power to detect a 15 percent treatment effect of high dose supplementation. In addition the study has at least 90 percent power to detect a 20 percent and 25 percent treatment effect in the stratified subgroups of vitamin supplementers and nonsupplementers, respectively.

Visual acuity. The effect of treatment on the rate of first occurrence of doubling of the visual angle due to cataract will also be tested. Event rates for this outcome are likely to be in the range of 20- or 30-percent (rates illustrated in Exhibit 3-15). An additional visual acuity event is the occurrence in an eye of a visual acuity score of < 35 (the uniocular analogue of legal blindness).

Analytic Methods. The design of the cataract clinical trial is a two-arm comparison with a dichotomous primary endpoint. Analytic methods to be used in the analysis of the clinical trial of cataract will include those described in Section 3.1.5.7.

3.4.2 AMD

The design of the clinical trial of AMD is illustrated in Exhibit 3-16. In the primary study of the AMD clinical trial, 3,600 AREDS participants with age-related macular changes (AMD Categories 2, 3, or 4, as defined in Section 3.1.2) will be randomized with 25-percent probability, in a factorial design, to daily oral supplements of antioxidants alone, zinc alone, antioxidants and zinc, or placebo. In a secondary study of the AMD clinical trial, the effect of antioxidants in all 4,600 participants, including those receiving zinc, will be evaluated (Exhibit 3-17).

3.4.2.1 Objectives. The objective of the AMD clinical trial is to answer the following three questions:

1. Does zinc or antioxidants reduce the incidence of advanced AMD in persons with age-related macular changes (AMD Categories 2, 3 and 4)?

2. Do antioxidants reduce the incidence or progression of macular abnormalities (e.g., type and size of drusen, pigment abnormalities)?

3. Is there a zinc-antioxidant interaction?

3.4.2.2 Study population. The 3,600 participants with age-related macular changes will form the cohort of primary analysis for the effect of high dose antioxidants and zinc. The entire cohort (4,600 participants) will be included in a secondary analysis of the effect of antioxidants on progression of AMD.

3.4.2.3 Outcome variables. The primary morphologic outcome of the clinical trial is the development of advanced macular degeneration (defined in Section 3.1.2) in at least one eye of participants with age-related macular changes when enrolled in the study. A secondary morphologic outcome is the development and progression of age-related macular changes. Two other outcome variables are noted below:

Visual acuity. A doubling of the visual angle (a loss of 15 or more letters) consistent with changes due to macular degeneration and inconsistent with other changes.

Toxicity. Morbidity and mortality events reported to be possibly related to study supplements on the Adverse Experience Report (Appendix C) will be classified as toxic outcomes. Imbalances

among treatment arms of (1) reported morbidity and mortality regardless of relationship to the study supplements, (2) hematocrit, and (3) serum cholesterol will also be reported.

3.4.2.4 Statistical considerations. For the clinical trial of AMD, 3,600 participants will be divided with equal probability into four study groups (placebo, antioxidants alone, zinc alone, and antioxidants plus zinc). The effects of antioxidants and of zinc on the development of advanced AMD are the main analyses to be performed. The interactions of antioxidants and zinc will also be evaluated.

Dropout and nonadherence. As in the clinical trial of cataract (Section 3.4.1.4), it is assumed that 15 percent of the participants will be lost to followup prior to experiencing an event. Additionally, for ease of presentation of power considerations of the factorial design, it is assumed that 80 percent of each group will adhere to their assigned study medication, 10 percent will take nothing, and 10 percent will take high dose nonstudy supplements (antioxidants and zinc). The rates of progression to advanced AMD for each treatment cohort in the factorial design are adjusted to reflect these estimates of nonadherence. The more complex model of nonadherence presented in Section 3.4.1.4 for the cataract study which assumes time-varying nonadherence is used for the power calculations for a two-arm comparison in the AMD studies.

Treatment effect and power considerations for factorial design. Unpublished data from Framingham Eye Study II, which reevaluated in 1986-1988 the patients whose eyes had been examined in 1973-1975, indicate that the 7-year incidence of advanced AMD would be about 1 to 2 percent among participants entering AREDS with few or no drusen, about 2 to 7 percent among participants with multiple small drusen or intermediate drusen, and about 7 to 14 percent among participants with at least one large drusen. Recent findings from a study by Bressler et al[27] indicate that, in persons with advanced AMD in one eye, the 7-year incidence of development of advanced AMD in the fellow eye is between 21 and 42 percent.

Using the above incidence data, one can estimate an overall 7-year incidence for the cohort of AREDS participants with age-related macular changes upon entering the study. Given a total of 3,600 participants (1,000 in Category 2 with intermediate drusen; 1,300 in Category 3 with at least one large drusen in one or both eyes and without advanced macular degeneration in either eye; and 1,300 in Category 4 with advanced AMD or visual loss in one eye only) and the estimated 7-year incidence for each AMD category, an estimate of the 7-year incidence for the entire cohort is 0.17 (Exhibit 3-18). In the absence of a treatment effect, the number of expected events in each AMD category, adjusting for loss to followup, is provided in Exhibit 3-19.

Assuming that 15 percent of the enrolled participants are lost to followup due to death and dropout, 3,060 participants randomized among the four study arms will be available for analysis. The sample size will provide nearly 80-percent power to detect decreases in this rate in at least one of the treatment arms for the four situations listed below. Note that these situations are not exhaustive.

Situation	Reduction	Due to
1	25	Antioxidants
	25	Zinc
	50	Antioxidants and zinc (no interaction)
2	40	Antioxidants
	40	Zinc
	40	Antioxidants and zinc (negative interaction)
3	0	Antioxidants
	40	Zinc
	0	Antioxidants and zinc (negative interaction)
4	0	Antioxidants
	35	Zinc
	35	Antioxidants and zinc (no interaction).

Exhibit 3-20 provides some examples of the approximate power of an overall test of no difference among the four treatment groups within this cohort. Power estimates in Exhibit 3-20 assume a two-sided $\alpha = 0.05$ test and, alternatively, a two-sided $\alpha = 0.01$ test, given a 0.17 rate of progression, varying rates of reduction in the treatment arms, and nonadherence rates of 10 percent in each treatment group as described above.

If an overall treatment effect is demonstrated, it will also be of interest to investigate the effect of high-dose supplemental antioxidants and zinc for persons with AMD believed to be at increased risk for development of advanced AMD. This group is likely to be comprised mostly of participants in AMD Categories 3 and 4. Excluding participants in AMD Category 2 from this analysis and assuming a 15-percent dropout, 2,200 participants will be available for analysis with an expected 0.20 progression rate at 7 years. Exhibit 3-21 provides power estimates for each of the four situations listed above.

Progression on the AMD Severity Scale. Photographic evidence of progression on the AMD severity scale (Exhibit 3-8) in at least one eye is a morphologic response variable for participants in drusen Category 1 or 2 at baseline. The scale in Exhibit 3-8 is based on data available at the start of AREDS. Modifications of this scale based on progression rates to severe AMD will be made as AREDS progresses. Because these modifications are based on data derived from within the study, this endpoint will be used as a secondary endpoint (i.e., more for hypothesis development than for hypothesis testing). Other secondary outcomes for progression of AMD include development of pigment abnormalities, increase in drusen area in one or both eyes, and development of large drusen. The effectiveness of zinc will be measured using the factorial design including only the 3,600 participants with age-related macular changes at randomization. Based on unpublished data from the Framingham II study, the event rates of these endpoints are likely to be higher than the rates of

development of advanced AMD, and the power of the tests will exceed 80 percent for the four situations described above.

Power considerations for 2-arm comparisons. In both the primary study that includes 3,600 participants with AMD at randomization and the secondary study that includes all 4,600 participants, the effectiveness of the antioxidants will be measured in a two-arm comparison of progression rates of macular changes. These changes will include not only progression to advanced AMD, but also such changes as development of pigment abnormalities, development of large drusen, and doubling of drusen area. Exhibit 3-22 summarizes different event rates of participants receiving placebo and various levels of treatment effects for which the study has 90 percent power to detect. The table assumes the following:

- two-arm comparisons
- no interaction
- a 1-year lag of treatment effect
- 15 percent of participants are lost before experiencing an event (lost to followup or death)
- 30 percent of participants assigned to placebo will begin to supplement with an equivalent of the active treatment as follows: 2 percent in each of years 1 and 2, 4 percent in each of years 3 and 4, and 6 percent in each of years 5, 6, and 7.
- 20 percent of participants assigned to active treatment will stop taking all treatment as follows: 2 percent in year 1, 1 percent in year 2, 2 percent in year 3, 3 percent in year 4, and 4 percent in each of years 5, 6, and 7.
- one-sided $\alpha = .025$
- 90-percent power
- 60 percent of participants will choose to take Centrum® (vitamins) at randomization.

The outcome in the primary AMD study is progression to advanced AMD (Section 3.1.2) among participants with nonadvanced AMD at randomization (AMD Category 2, 3, and 4). A total of 3,600 participants will initially be available for analysis for this outcome. Assuming 15 percent of participants are lost prior to experiencing an event, 3,060 participants will be available for analysis at 7 years or will have experienced an event prior to loss; 1,836 vitamin supplementers, 1,224 nonsupplementers. The event rate for the primary outcome is expected to be around 20 percent. The study has at least 90-percent power to detect a 30 percent treatment effect overall and a 40 percent and 50 percent treatment effect within the vitamin user and no vitamin user strata.

In addition to the primary outcome, a surrogate outcome, development or progression of AMD, will be analyzed. All 4,600 participants will initially be available for this analysis. As above, assuming 15 percent are lost to followup, 3,910 participants will be analyzed; 2,346 vitamin

supplementers, 1,564 non supplementers. The event rate for the surrogate outcome is expected to be between 30 and 50 percent for all participants randomized to placebo. If the event rate of this surrogate outcome is 30 percent, the study will have at least 90 percent power to detect a 25 percent treatment effect overall and a 30 percent and 35 percent treatment effect within the vitamin users and nonvitamin users respectively. If the event rate of this surrogate outcome is 50 percent, the study has at least 90 percent power to detect a 15 percent treatment effect of high dose supplementation, and a 20 percent and 25 percent treatment effect in the stratified subgroups of vitamin supplements and nonsupplementers, respectively.

Visual acuity. Smiddy and Fine[28] retrospectively studied patients with bilateral drusen reporting that the 5-year cumulative risk of clinically important loss of visual acuity from exudative maculopathy was 12.7 percent. This percentage is likely to be a high estimate based on the morphologic estimates derived from Framingham II and the study by Bressler et al.[27] It is anticipated that the rate of a visual acuity event will be lower than the rate assumed for the morphologic endpoints. Unless Smiddy and Fine[28] are correct, the power to detect treatment differences using this visual acuity endpoint will be lower than the power provided to test the morphologic endpoints.

Toxicity monitoring. To date, little is known about the toxicity associated with long-term use of nutritional supplements. Anemia, which has been shown to be associated with ingestion of zinc but readily reversed by copper supplementation, will be monitored by performing baseline and annual measurements of hematocrit on all participants. In addition, there have been conflicting reports on the effect of zinc on cholesterol. Serum cholesterol will be measured annually in approximately 1,020 study participants (400 participants assigned to treatment including high doses of zinc, and 620 participants assigned to treatment without high doses of zinc). These sample sizes will provide 90-percent power to detect a change in serum cholesterol of 10 mg/dl assuming a two-sided $\alpha = .05$ level test. Imbalances among treatments of reported morbidity and mortality will also be monitored and reported. Interim analyses will be performed to evaluate the data with respect to the toxicity of the supplements.

Analytic methods. The design of the AMD clinical trial is a 2^2 factorial with a dichotomous primary endpoint. An overall test of no difference among the four treatment groups will be performed using the chi-square statistic. The test has three degrees of freedom and, if significant, will be followed by multiple comparisons to describe the differences among the four treatment groups. Other analytic methods to be used in the analysis of the clinical trial of AMD will include those described in Section 3.1.5.7.

3.4.3 Cardiovascular disease, Cancer, and Mortality

The impact of antioxidants on the mortality rate from ischemic heart disease, non-fatal rate from ischemic heart disease, incidence rate of cancer and mortality rates from all causes will be assessed. Information on cause of hospitalization, diagnosis of cancer, and cause of death is required as part of routine AREDS followup. Rates of such events among the AREDS population are expected to be 2 to 10 percent after seven years of followup. The size of treatment effect for which AREDS will have 80-percent power to detect is calculated assuming the following:

- No interaction

- Two-arm comparisons
- one-sided $\alpha = .025$
- 1-year treatment effect lag
- 15 percent loss to followup or death prior to event
- Drop in rate 30 percent: 2 percent each of years 1 and 2, 4 percent each of years 3 and 4, 6 percent each of years 5, 6, and 7.
- 20 percent of high dose supplementers quit taking their supplements: 2 percent year 1, 1 percent of year 2, 2 percent of year 3, 3 percent of year 4, 4 percent each of years 5, 6, and 7.
- Sample size of 3,910 after adjustment for 15 percent losses to followup and deaths.

AREDS will have 80-percent power to detect a 35-percent treatment effect if the event rate for placebo is .10, a 45-percent treatment effect if the event rate for placebo is .06 and a 70-percent treatment effect if the event rate for placebo is .02.

3.5 REFERENCES

1. Ederer F: Shall we count eyes or subjects? *Arch Ophthalmol* 89:1–2, 1973.
2. Katz J: Two eyes or one? The data analyst's dilemma. *Ophthalmic Surg* 19:585–589, 1988.
3. Milton RC, Ederer F: Partially paired designs. *Biometrics Note* No. 5. Office of Biometry and Epidemiology, National Eye Institute, National Institutes of Health, Bethesda, Maryland, May 1974.
4. Kahn HA: Letter. *Invest Ophthalmol* 13:634–635, 1974.
5. Rosner B: Statistical methods in ophthalmology: An adjustment for the intraclass correlation between eyes. *Biometrics* 38:105–114, 1982.
6. Seigel D, Podgor M: A sign test for survivorship curves. *Controlled Clin Trials* 3:69–71, 1982.
7. Ray WA, O'Day DM: Statistical analysis of multi-eye data in ophthalmic research. *Invest Ophthalmol Vis Sci* 26:1186–1188, 1985.
8. Le CT: Testing for linear trends in proportions using correlated otolaryngology or ophthalmology data. *Biometrics* 44:299–303, 1988.

9. Newcombe RG, Duff GR: Eyes or patients? Traps for the unwary in the statistical analysis of ophthalmological studies. *Br J Ophthalmol* 71(9):645–646, 1986.

10. Pocock SJ, Geller NL, Tsiatis AA: The analysis of multiple endpoints in clinical trials. *Biometrics* 43:487–498, 1987.

11. James S: Approximate multinormal probabilities applied to correlated multiple endpoints in clinical trials. *Stat Med* 10:1123–1135, 1991.

12. DeMets DL, Hardy R, Friedman LM, Lan KKG: Statistical aspects of early termination in the beta-blocker heart attack trial. *Controlled Clin Trials* 5:362–372, 1984.

13. Fleming TR, Harrington DP, O'Brien PC: Designs for group tests. *Controlled Clin Trials* 5:348–361, 1984.

14. Lan KKG, DeMets DL: Discrete sequential boundaries for clinical trials. *Biometrika* 70:659–664, 1983.

15. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. *Biometrics* 35:549–556, 1979.

16. Lan KKG, Lachin JM: Implementation of group sequential logrank tests in a maximum duration trial. *Biometrics* 46:759–770, 1990.

17. Lan KKG, DeMets DL: Discrete sequential boundaries for clinical trials. *Biometrika* 70:659–663, 1983.

18. Reboussin DM, DeMets DL, Kim K-M, Lan KKG: Programs for computing group sequential bounds using the Lan-DeMets method. Technical Report #60, University of Wisconsin Department of Biostatistics, 1992.

19. Pocock SJ: Group sequential methods in the design and analysis of clinical trials. *Biometrika* 64:191–199, 1977.

20. Wei LJ, Lachin JM: Two sample asymptotically distribution-free tests for incomplete multi-variate observations. *JASA* 79:653–661, 1984.

21. Early Treatment Diabetic Retinopathy Study Research Group: Photocoagulation for macular edema. *Arch Ophthalmol* 103:1796–1806, 1985.

22. Choi SC, Stablein DM: Comparing proportions with incomplete data under non-random mechanisms. *Stat Med* 7:929–939, 1988.

23. Liang KY, Zeger SL: Longitudinal data analysis using generalized linear models. *Biometrika* 80:55–61, 1986.

24. Qaqish BF, Liang K-Y: Marginal models for correlated binary responses with multiple classes and multiple levels of nesting. *Biometrics* 48:939–950, 1992.

25. Wei LJ, Lin DY, Weissfeld L: Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *J Am Stat Assoc* 84:1065–1073, 1989.

26. Lee EW, Wei LJ, Amato DA: Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In *Survival Analysis: State of the Art,* JP Klein, PK Goel (eds.) Dordrecht: Kluwer Academic Publishers, 237–247, 1992.

27. Bressler SB, Maguire MG, Bressler NM, Fine SL, The Macular Photocoagulation Study Group: Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration. *Arch Ophthalmol* 108:1442–1447, 1990.

28. Smiddy WE, Fine SL: Prognosis of patients with bilateral macular drusen. *Ophthalmol* 91:271–277, 1984.

Exhibit 3-1. STUDIES OF CLINICAL COURSE AND RISK FACTORS

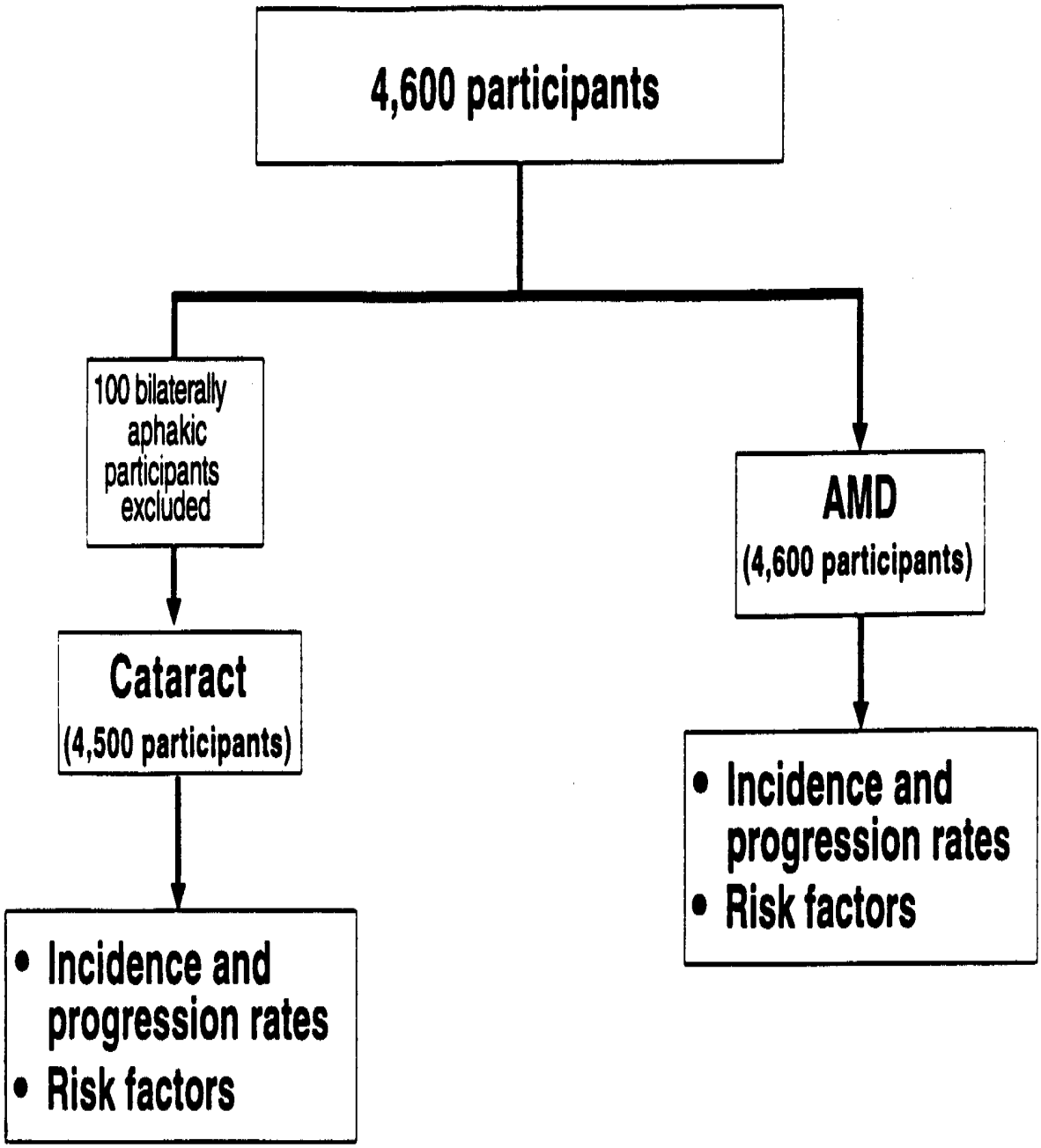


Exhibit 3-2. CLINICAL TRIALS OF CATARACT AND AMD

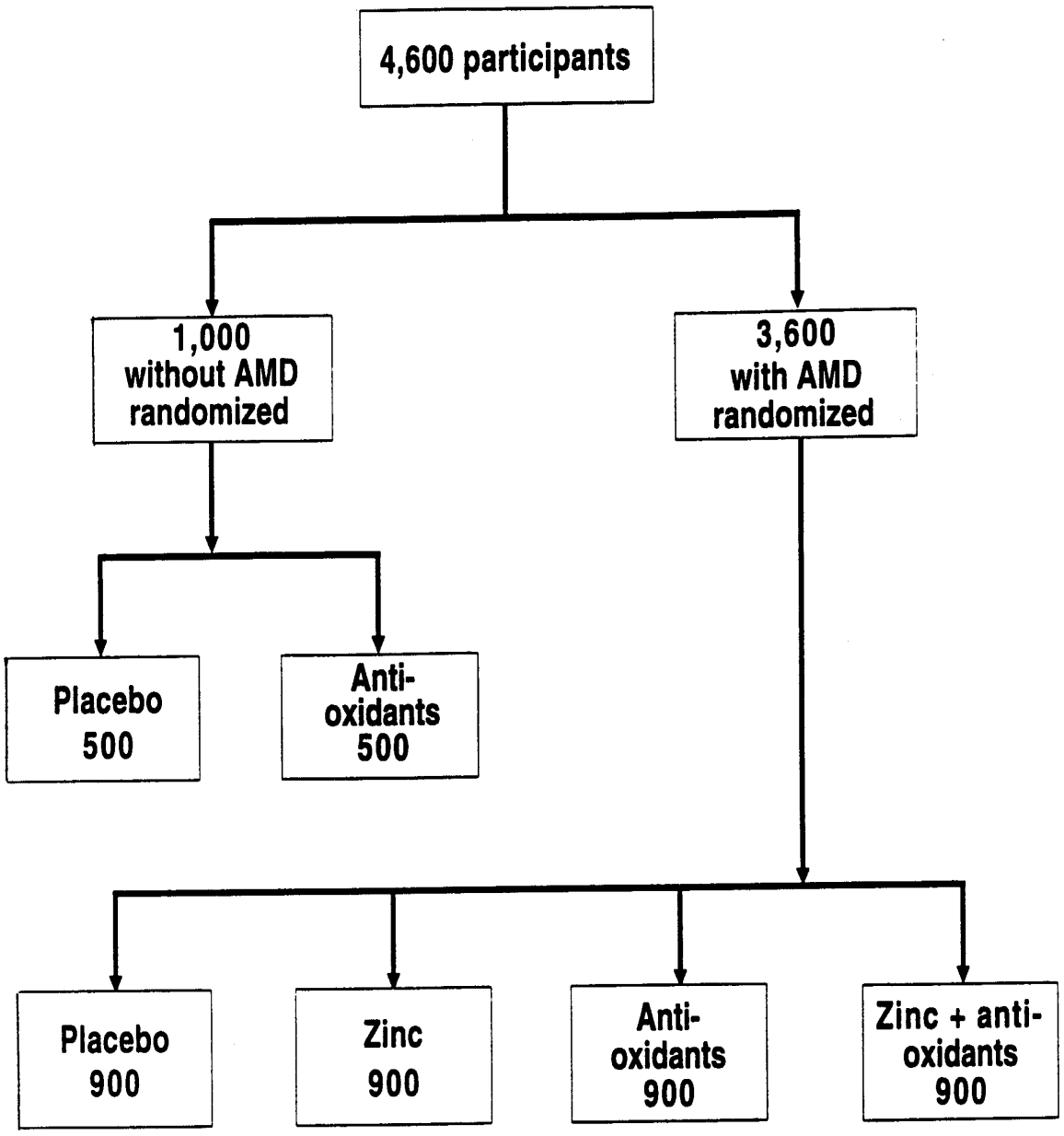


Exhibit 3-3. AREDS LENS OPACITY GRADING SYSTEM

NUCLEAR OPALESCENCE

Using a decimalized scale, the unknown slit lamp photograph is placed into the appropriate interval between two of seven standard slit lamp photographs. For example, an unknown four tenths of the way between Std 4 and Std 5 would receive the grade 4.4.

Grade	Severity compared to standard photographs	Cataract
0.9	< that in Slit Lamp Std 1	None
1.0	= that in Slit Lamp Std 1	None
2.0	= that in Slit Lamp Std 2	Very mild
3.0	= that in Slit Lamp Std 3	Mild
4.0	= that in Slit Lamp Std 4	Moderate
5.0	= that in Slit Lamp Std 5	Severe
6.0	= that in Slit Lamp Std 6	Very severe
7.0	= that in Slit Lamp Std 7	Extremely severe
7.1	> that in Slit Lamp Std 7	Extremely severe

The grades are then rescaled at the Coordinating Center by converting original grade 2.0 to a score of 1.5, grade 3.0 to a score of 2.0, 4.0 to 3.0, etc. This rescaling, based on mapping the original grades in the interval [1.0,3.0] to the interval [1.0, 2.0], is thought to provide a more uniform progression of opacity.

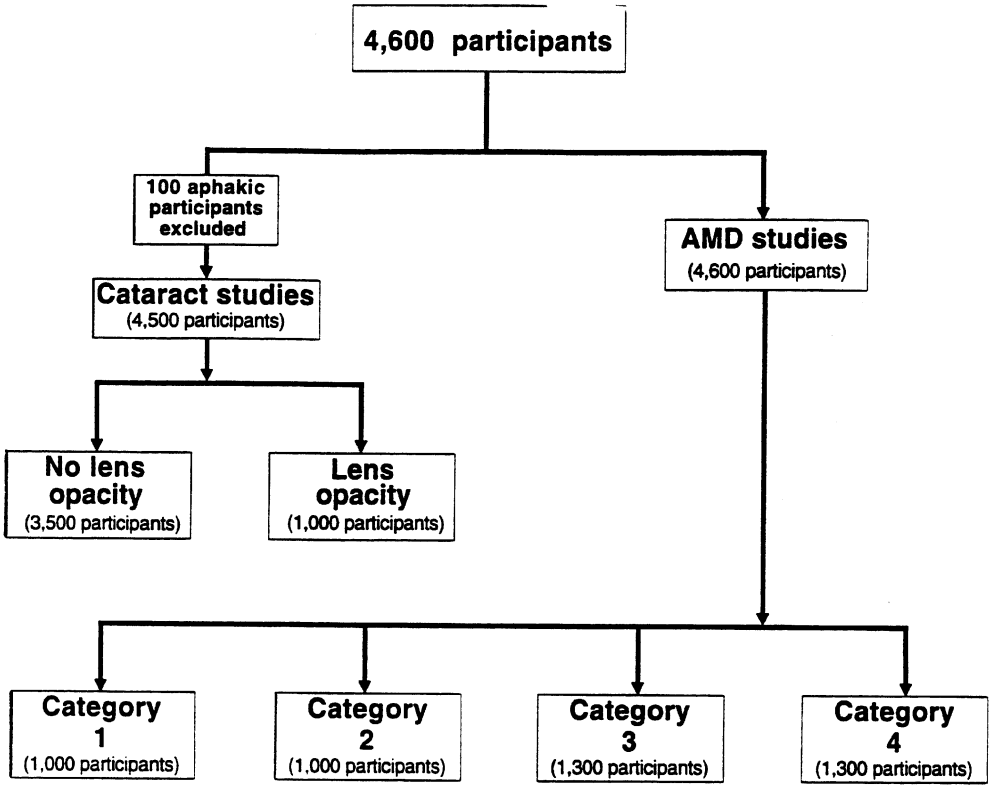
CORTICAL OPACITY AND POSTERIOR SUBCAPSULAR OPACITY

After the unknown Neitz retro-illuminated photograph is divided into subfields by application of a grid (consisting of the central subfield with 2 mm diameter, eight radiating sectors from the central subfield to the 5 mm diameter, and eight radiating sectors from the 5 mm diameter to the pupillary margin). Separately for cortical and posterior subcapsular opacities, the percent of each subfield involved by cataract is estimated. Weighting the estimates for each subfield according to its area, these results are combined into percent involvement for a standardized region of observation likely to be visible at all visits (all subfields within the 5 mm diameter) and for the entire area of lens visible at all visits (all subfields). It is anticipated that both cortical and posterior subcapsular opacities will be analyzed as continuous variables. If a categorical scale is used for some analyses, the following steps (from the Beaver Dam Eye Study) are suggested.

Percentage of standardized area (within 5 mm circle) with cortical opacity	Cataract
0	None
1-5	Questionable
6-25	Early
26-100	Late

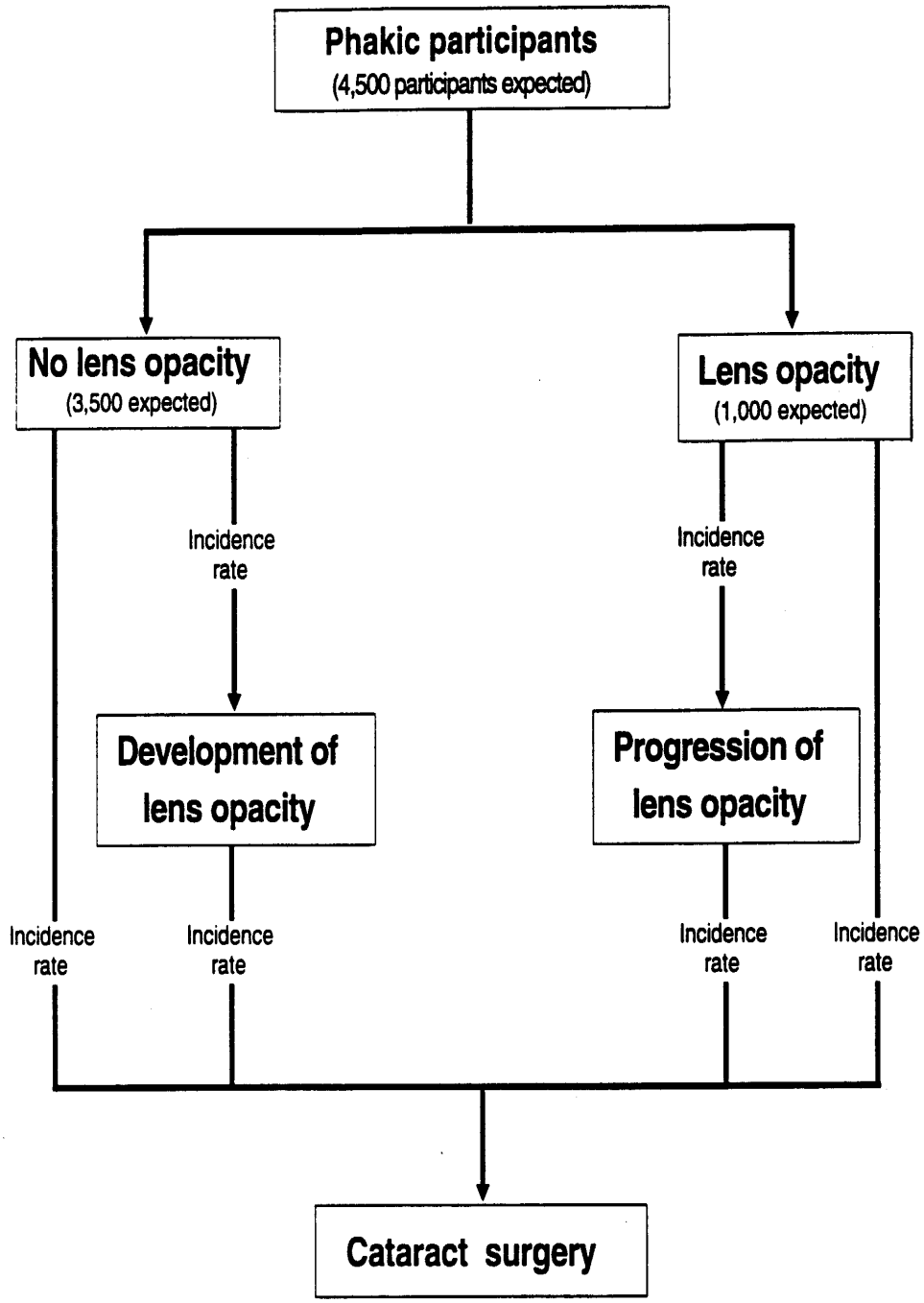
Percentage of central area (within 2 mm circle) with posterior subcapsular opacity	Cataract
0	None
1-5	Questionable
6-25	Early
26-100	Late

Exhibit 3-4. STUDY POPULATION GOAL FOR STUDIES OF CATARACT AND AMD



Lens opacity and AMD Categories are defined in Section 3.1.2.

Exhibit 3-5. CLINICAL COURSE AND PROGNOSIS — CATARACT



Note: The term "incidence" encompasses both incidence and progression.

Exhibit 3-6. 95-PERCENT CONFIDENCE INTERVALS FOR VARIOUS INCIDENCE AND PROGRESSION RATES FOR LENS OPACITY, BY STUDY POPULATION

Study population	Observed rate	95-percent confidence interval	
No lens opacity		**All (n = 3,500)**	**Placebo only[1] (n = 1,750)**
	0.02	0.015, 0.025	0.013, 0.027
	0.05	0.043, 0.057	0.040, 0.060
	0.10	0.090, 0.110	0.086, 0.114
	0.15	0.138, 0.162	0.133, 0.167
	0.20	0.187, 0.213	0.181, 0.219
	0.25	0.236, 0.264	0.230, 0.270
	0.30	0.285, 0.315	0.279, 0.321
	0.40	0.384, 0.416	0.377, 0.423
	0.50	0.483, 0.517	0.477, 0.523
Some lens opacity		**All (n = 1,000)**	**Placebo only[1] (n = 500)**
	0.02	0.011, 0.029	0.008, 0.032
	0.05	0.036, 0.064	0.031, 0.069
	0.10	0.081, 0.119	0.074, 0.126
	0.15	0.128, 0.172	0.119, 0.181
	0.20	0.175, 0.225	0.165, 0.235
	0.25	0.223, 0.277	0.212, 0.288
	0.30	0.272, 0.328	0.260, 0.340
	0.40	0.370, 0.430	0.357, 0.443
	0.50	0.469, 0.531	0.456, 0.544

[1] Includes participants assigned to zinc or placebo.

Exhibit 3-7. CLINICAL COURSE AND PROGNOSIS — AMD

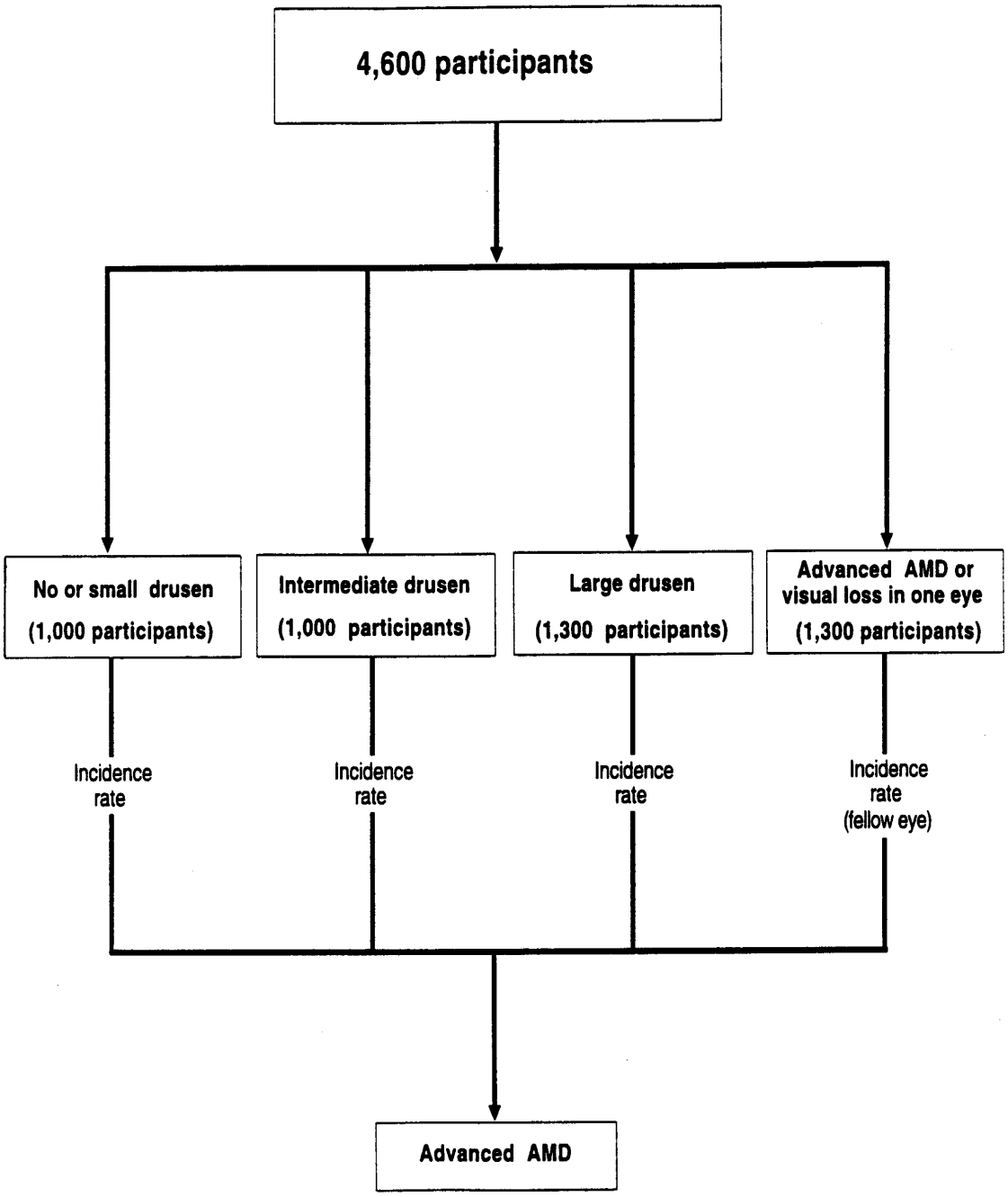


Exhibit 3-8. AMD SEVERITY SCALE

Level	Criteria
1	Drusen absent or questionable or small hard drusen present, total drusen area < circle C1 (125 microns diameter), without pigment abnormalities(PA).
2	Small hard drusen present, total drusen area ≥ circle C1, without PA.
3	(a) Drusen absent or questionable or small hard drusen present, total drusen area < circle C1, with PA, or (b) small drusen present, total drusen area ≥ circle C1, with PA.
4	(a) Intermediate or large drusen present, total drusen area < circle O2 (644 microns diameter), without indistinct soft drusen and without PA, or (b) intermediate or large drusen present, total drusen area < circle I2 (350 microns diameter), with indistinct soft drusen and without PA.
5	(a) Intermediate or large drusen present, total drusen area < circle O2, without indistinct soft drusen and with PA, or (b) intermediate or large drusen present, total drusen area < circle I2, with indistinct soft drusen and with PA.
6	(a) Intermediate or large drusen present, total drusen area ≥ circle O2, without indistinct soft drusen and without PA, or (b) intermediate or large drusen present, total drusen area ≥ circle I2, with indistinct soft drusen and without PA.
7	(a) Intermediate or large drusen present, total drusen area ≥ circle O2, without indistinct soft drusen and with PA, or (b) intermediate or large drusen present, total drusen area ≥ circle I2, with indistinct soft drusen and with PA.
8	(a) Geographic atrophy definitely present within 2 DD of the center of the macula, or (b) geographic atrophy definitely present within 500 μm of the center of the macula (the central subfield).
9	(a) Geographic atrophy definitely present in the central subfield and questionably involving the center point of the macula, or (b) geographic atrophy definitely involving the center point of the macula.
10	Non-drusenoid pigment epithelial detachment or serous/hemorrhagic sensory retinal detachment in Field 2.
11	(a) Subretinal or sub-RPE hemorrhage, or subretinal fibrosis, in Field 2. (b) Photocoagulation scars consistent with treatment of AMD.

[1] Drusen characteristics are considered only in the region within 2 disc diameters (DD) of the center of the macula.

[2] Pigment abnormalities (PA) are defined as one or more of the following within the "central zone," i.e., within 1 DD of the center of the macula:

(a) Retinal pigment epithelial (RPE) depigmentation definitely present, or
(b) increased pigmentation ≥ standard circle C1 in extent (125 microns diameter), or
(c) RPE depigmentation questionably present and increased pigmentation definitely present but < circle C1 in extent.

Exhibit 3-9. 95-PERCENT CONFIDENCE INTERVALS FOR VARIOUS INCIDENCE AND PROGRESSION RATES FOR AMD, BY STUDY POPULATION

Study population	Observed rate	95-percent confidence interval	
AMD Category 1		**All (n = 1,000)**	**Placebo only (n = 500)**
	0.02	0.011, 0.029	0.008, 0.032
	0.08	0.063, 0.097	0.056, 0.104
	0.14	0.118, 0.162	0.110, 0.170
	0.20	0.175, 0.225	0.165, 0.235
AMD Category 2		**All (n = 1,000)**	**Placebo only (n = 250)**
	0.04	0.028, 0.052	0.016, 0.064
	0.10	0.081, 0.119	0.063, 0.137
	0.16	0.136, 0.184	0.115, 0.205
	0.20	0.175, 0.225	0.150, 0.250
AMD Category 3 or 4		**All each group (n = 1,300)**	**Placebo only each group (n = 325)**
	0.04	0.029, 0.051	0.019, 0.061
	0.16	0.140, 0.180	0.120, 0.200
	0.28	0.256, 0.304	0.231, 0.329
	0.40	0.373, 0.427	0.347, 0.453

Exhibit 3-10. RELATIVE RISKS DETECTABLE WITH 90-PERCENT POWER FOR RISK FACTOR STUDY OF CATARACT

	Participants expected to have characteristic at baseline		Relative risk[1]		
			Rate		
Risk factor[2]	Number[3]	Proportion	0.10	0.20	0.30
AMD Category 3 or 4	2,125	0.56	1.4	1.3	1.2
AMD Category 4	1,063	0.28	1.6	1.4	1.3
Presence of minimal lens opacity	850	0.22	1.7	1.4	1.3
History of cardiovascular disease	765	0.20	1.7	1.5	1.4
Current cigarette use	497	0.13	1.9	1.6	1.4
Alcohol use	2,295	0.60	1.4	1.3	1.2
Medication use	383	0.10	2.0	1.7	1.5
Light exposure	956	0.25	1.6	1.4	1.3
Sex (F)	2,295	0.60	1.4	1.3	1.2
Race (B)	153	0.04	3.0	2.0	1.8
History of vitamin use	1,913	0.50	1.5	1.3	1.2
Nutritional status poor		383	0.10	2.0	1.71.5
Diabetes	383	0.10	2.0	1.7	1.5
History of any skin cancer	1,530	0.40	1.5	1.3	1.3
Low serum antioxidants[4]	251	0.20	2.5	1.8	1.6

[1] Relative risks are calculated by risk factor and incidence or progression rate of lens opacity in participants without the risk factor at baseline: 4,500 participants, two-sided $\alpha = 0.01$.

[2] Listed on Baseline Interview Form

[3] Expected number less 15 percent for deaths and dropouts

[4] Three Clinical Centers and NEI Clinical Center

Exhibit 3-11. RELATIVE RISKS DETECTABLE WITH 90-PERCENT POWER FOR RISK FACTOR STUDY OF AMD

	Participants expected to have characteristic at baseline		Relative risk[1]		
				Rate	
Risk factor[2]	Number[3]	Proportion	0.10	0.20	0.30
AMD Category 3 or 4	2,210	0.57	1.4	1.3	1.2
AMD Category 4	1,105	0.28	1.6	1.4	1.3
AMD Category 2	850	0.22	1.7	1.4	1.3
AMD Category 1	850	0.22	1.7	1.4	1.3
Lens opacity baseline	850	0.22	1.7	1.4	1.3
Iris color (blue)	1,329	0.34	1.5	1.4	1.3
History of cardiovascular disease	782	0.20	1.7	1.5	1.4
Current cigarette use	508	0.13	1.9	1.6	1.4
Alcohol use	2,346	0.60	1.4	1.3	1.2
Medication use	391	0.10	2.0	1.7	1.5
Light exposure	978	0.25	1.6	1.4	1.3
Sex (F)	2,346	0.60	1.4	1.3	1.2
Race (B)	156	0.04	3.0	2.0	1.8
History of vitamin use	1,955	0.50	1.5	1.3	1.2
Nutritional status (poor)	391	0.10	2.0	1.7	1.5
Diabetes	391	0.10	2.0	1.7	1.5
History of any skin cancer	1,564	0.40	1.5	1.3	1.3
Educational status (Grade 12 or more)	2,933	0.75	1.4	1.3	1.2
Estrogen use (females only)	891	0.38	1.6	1.4	1.3
Elevated total cholesterol[4]	251	0.20	2.5	1.8	1.6
Low serum zinc[4]	251	0.20	2.5	1.8	1.6
Low serum antioxidants[4]	251	0.20	2.5	1.8	1.6

1 Relative risks are calculated by risk factor and incidence or progression rate of AMD in participants without the risk factor at baseline: 4,600 participants, two-sided $\alpha = 0.01$.

2 Listed on Baseline Interview Form

3 Expected number less 15 percent for deaths and dropouts

4 Three Clinical Centers and NEI Clinical Center

Exhibit 3-12. CLINICAL TRIALS OF CATARACT AND AMD

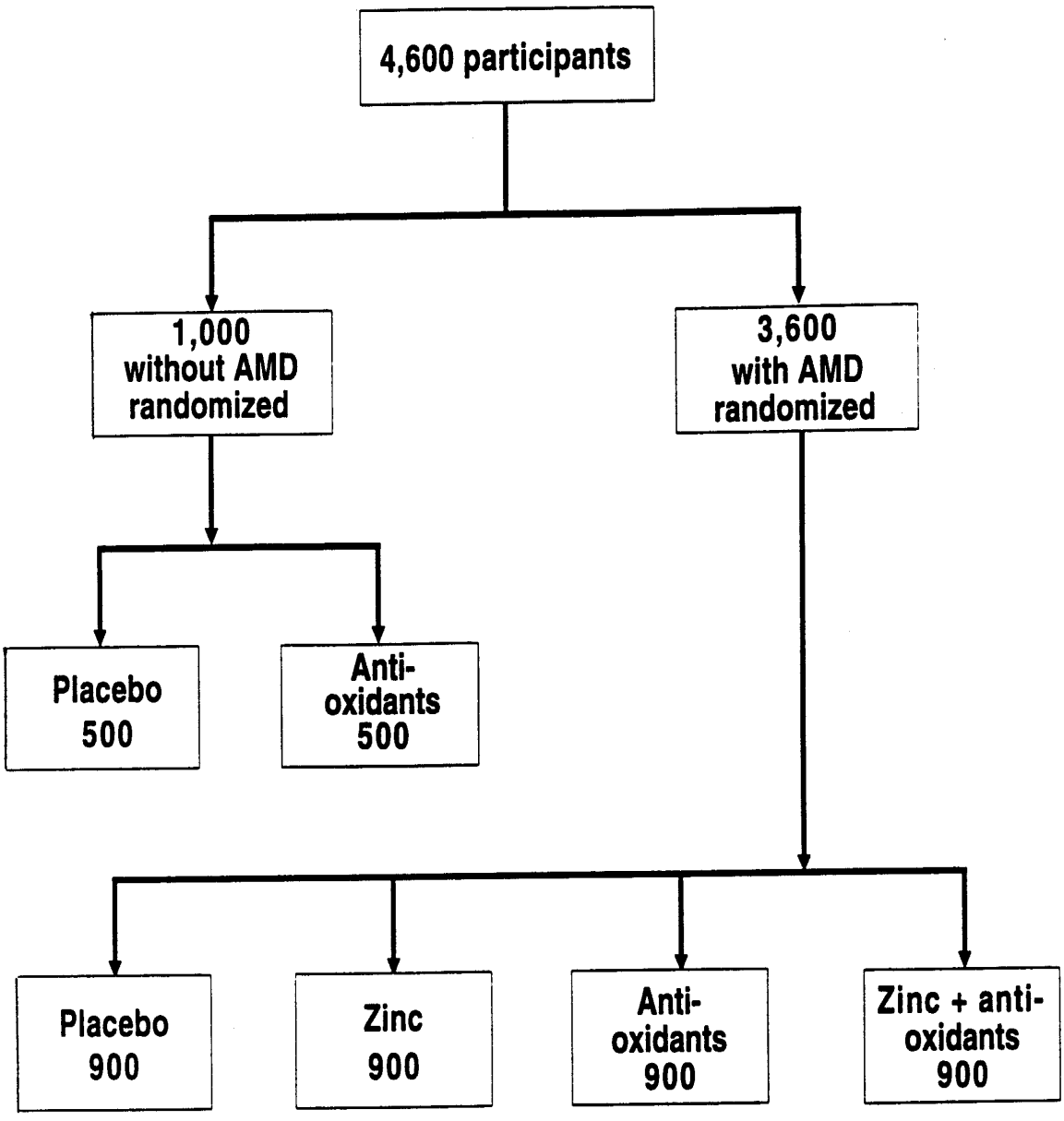
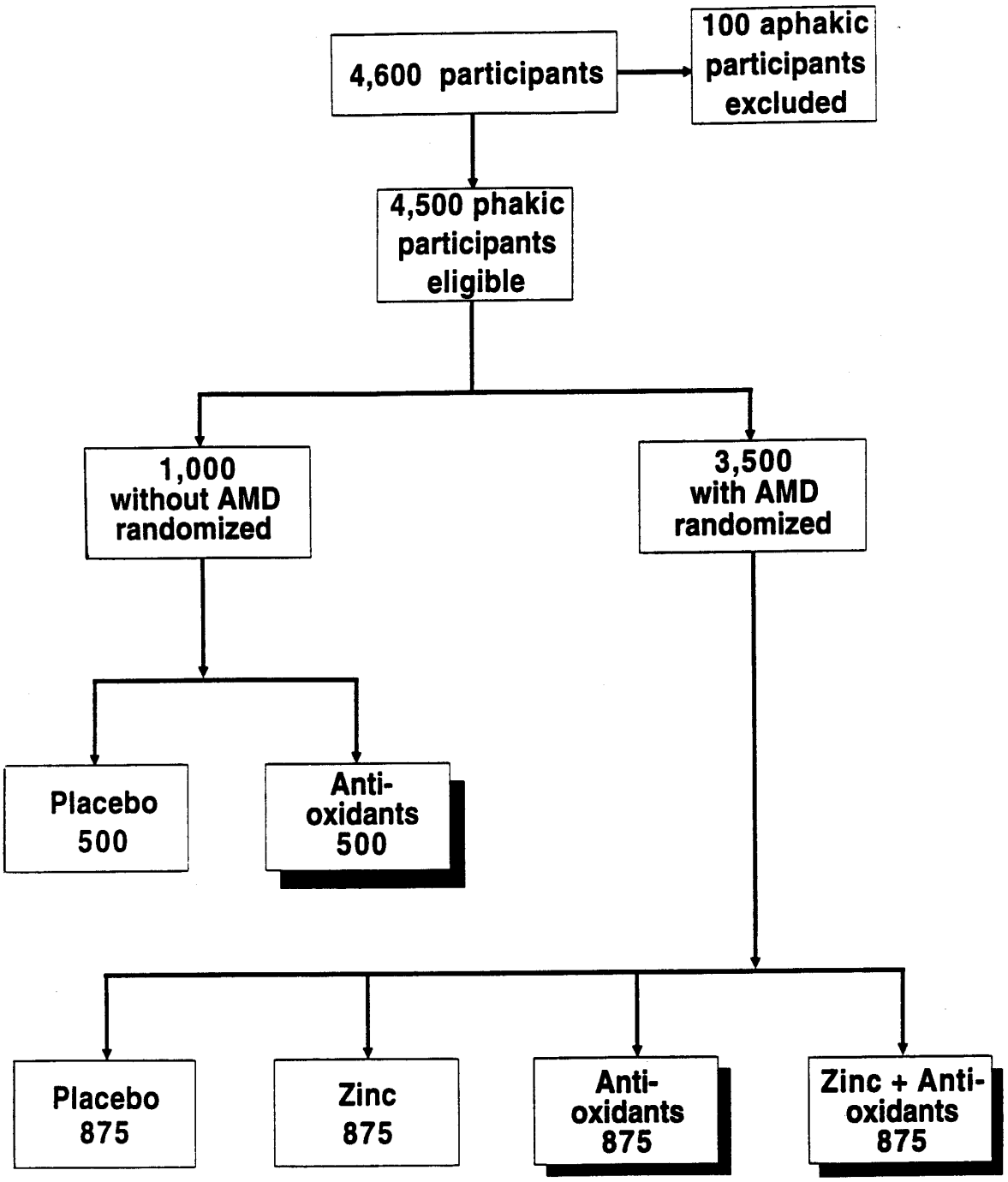


Exhibit 3-13. CLINICAL TRIAL — CATARACT



Note: 2,250 participants are assigned to antioxidants (shadowed boxes).
2,250 are not assigned to antioxidants (unshadowed boxes).

Exhibit 3-14. CLINICAL TRIAL — CATARACT
Numbers of Expected Events

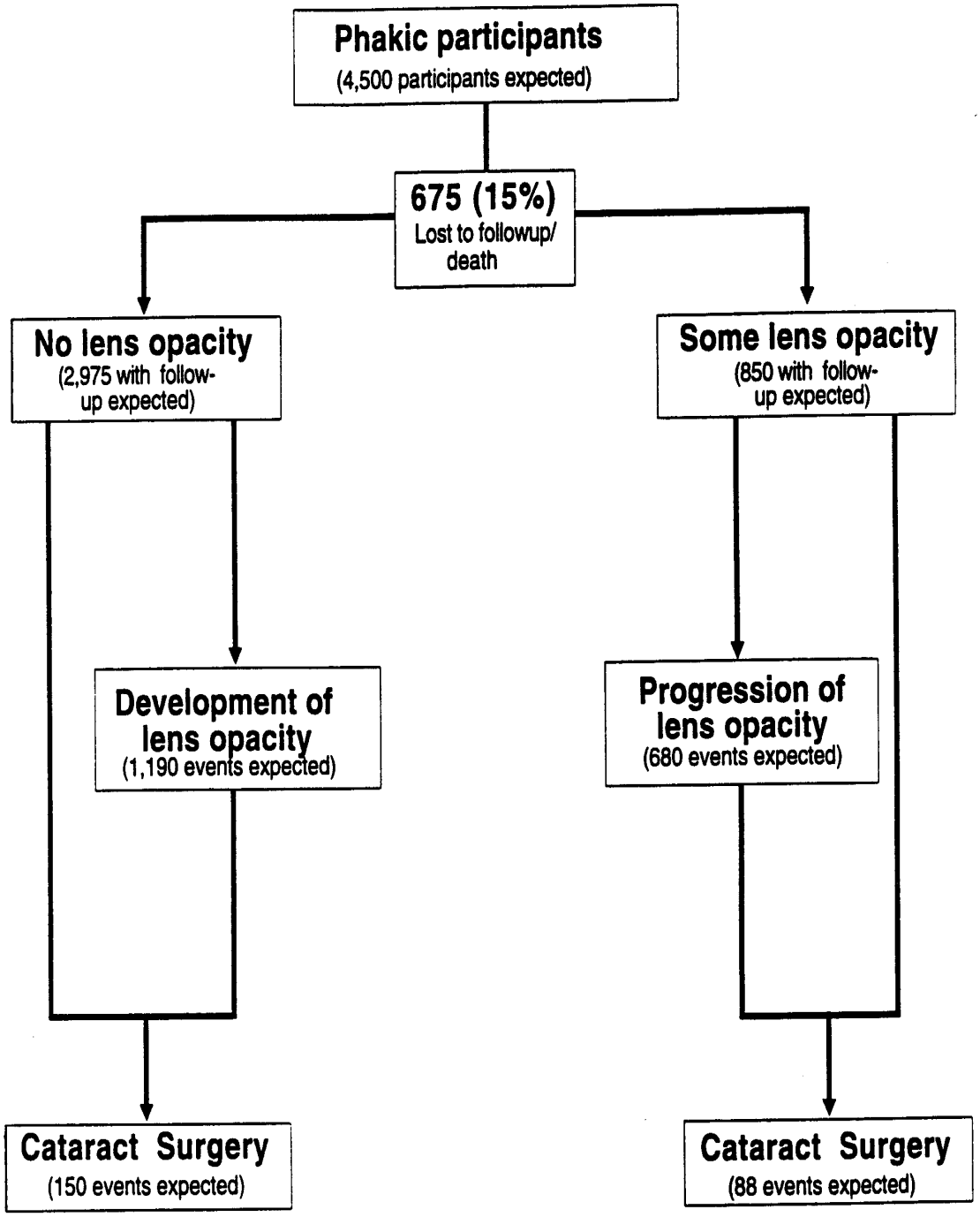


Exhibit 3-15. APROXIMATE TREATMENT EFFECTS (PERCENT REDUCTION) DETECTABLE WITH AT LEAST 90 PERCENT POWER BY PLACEBO EVENT RATE AND ANALYSIS GROUP FOR CATARACT TRIAL[1]

Analysis group	Sample size available[2] Number	Placebo event rate .50 Percent reduction	.30 Percent reduction	.20 Percent reduction
Cataract				
Total	3,825	15	25	30
Centrum®	2,295	20	30	35
No Centrum®	1,530	25	35	45

[1] Table assumes:

- No interaction
- Two-arm comparisons
- One-sided $\alpha = .025$
- 1 year treatment effect lag
- 15-percent lost to followup or death prior to event
- 60 percent choose to supplement with vitamins
- Dropin rate 30 percent: 2 percent each of years 1 and 2, 4 percent each of years 3 and 4, 6 percent each of years 5, 6, and 7.
- Dropout rate 20 percent: 2 percent year 1, 1 percent of year 2, 2 percent of year 3, 3 percent of year 4, 4 percent each of years 5, 6, and 7.

[2] Sample size adjusted for 15 percent losses to followup and deaths

Exhibit 3-16. CLINICAL TRIAL — AMD

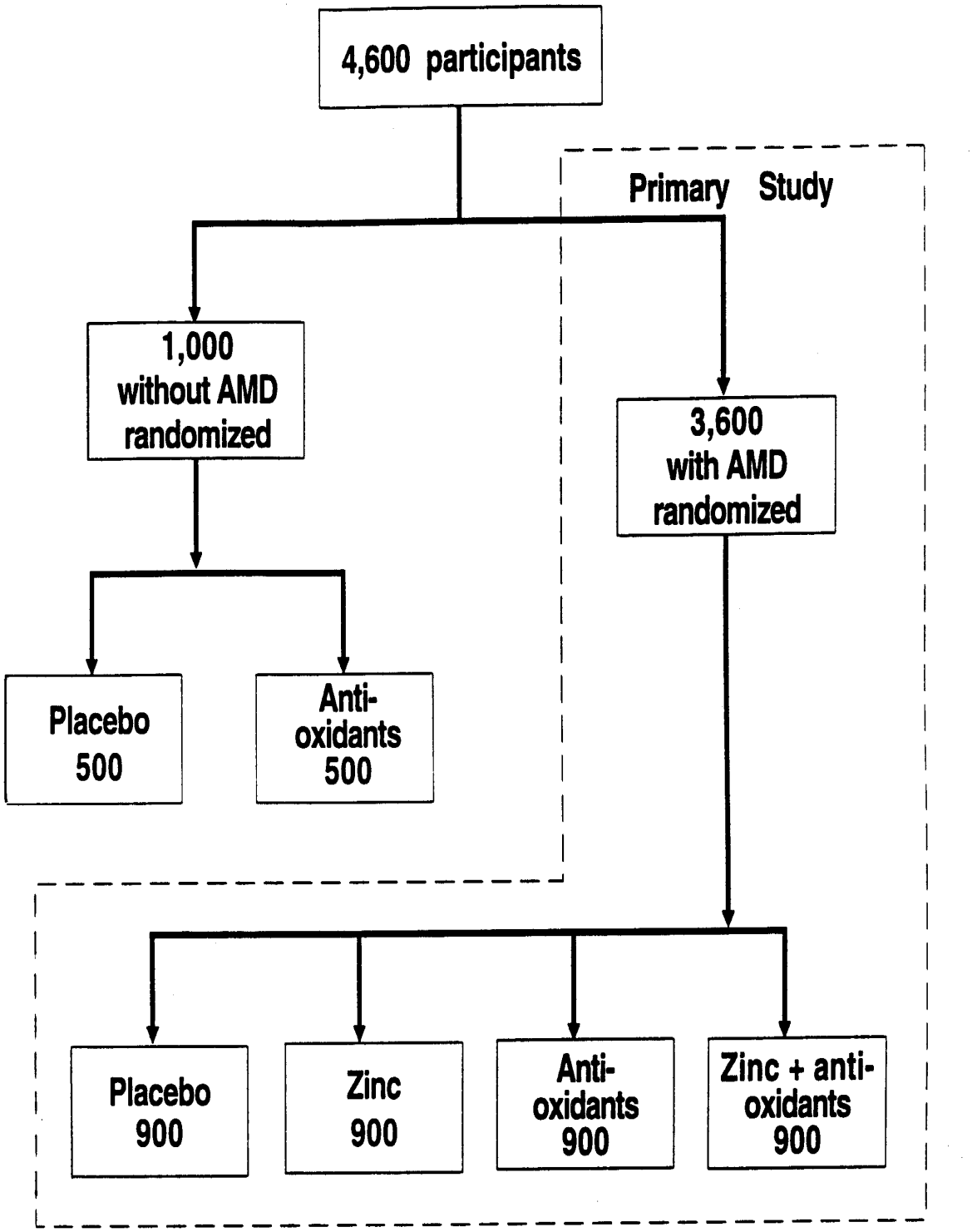


Exhibit 3-17. CLINICAL TRIAL — AMD
Secondary Study

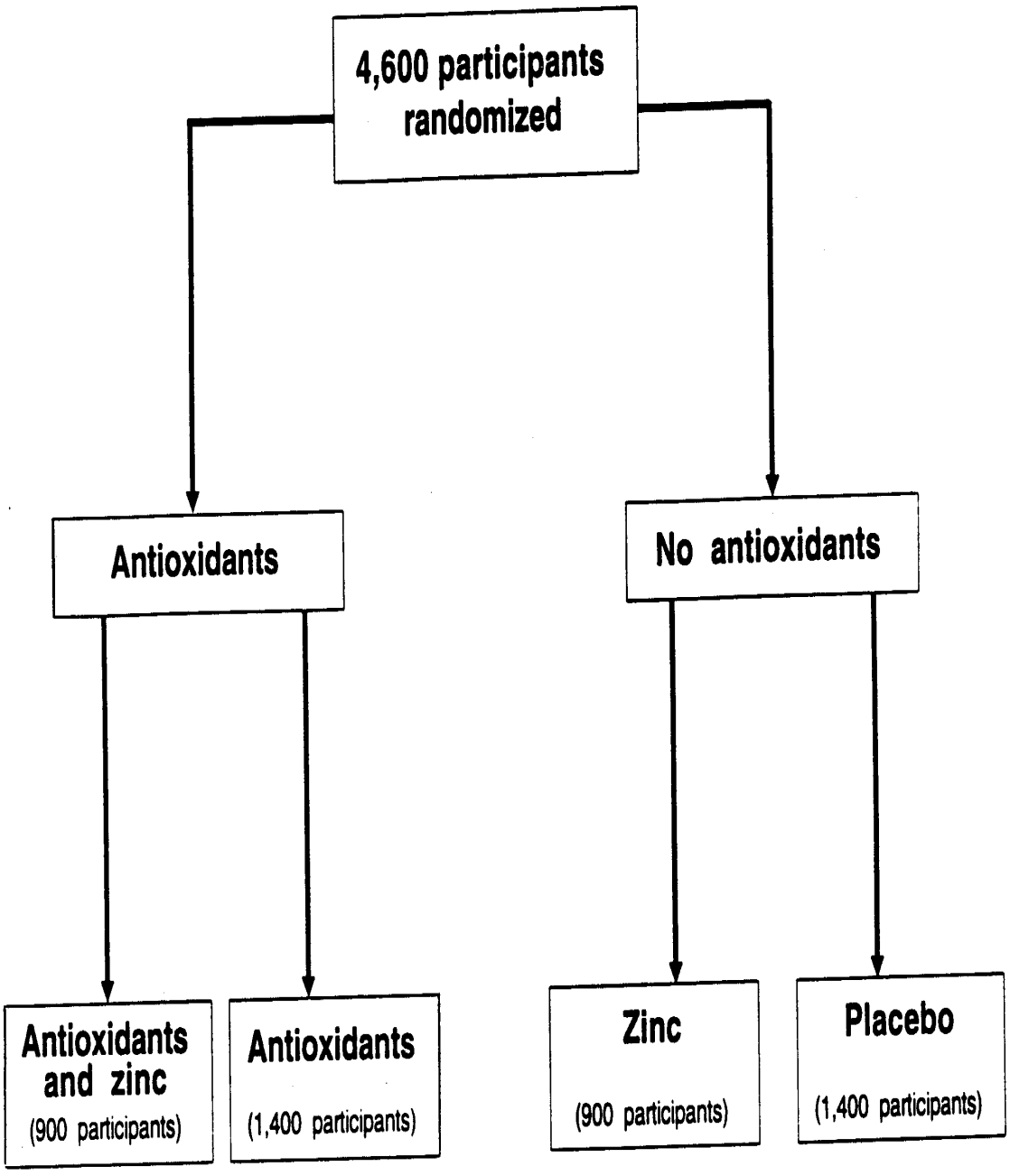


Exhibit 3-18. RATE OF PROGRESSION TO ADVANCED AMD

AMD Category	Number of participants enrolled	Number of participants with event or 7-year followup	Event rate		Number of events expected at 7 years
			Per year	7 years	
2	1,000	850	0.01	0.07	60
3	1,300	1,105	0.02	0.14	155
4	1,300	1,105	0.04	0.28	309
Total	3,600	3,060	0.023	0.17	524

Exhibit 3-19. CLINICAL TRIAL — AMD
Number of Expected Events in Primary Study

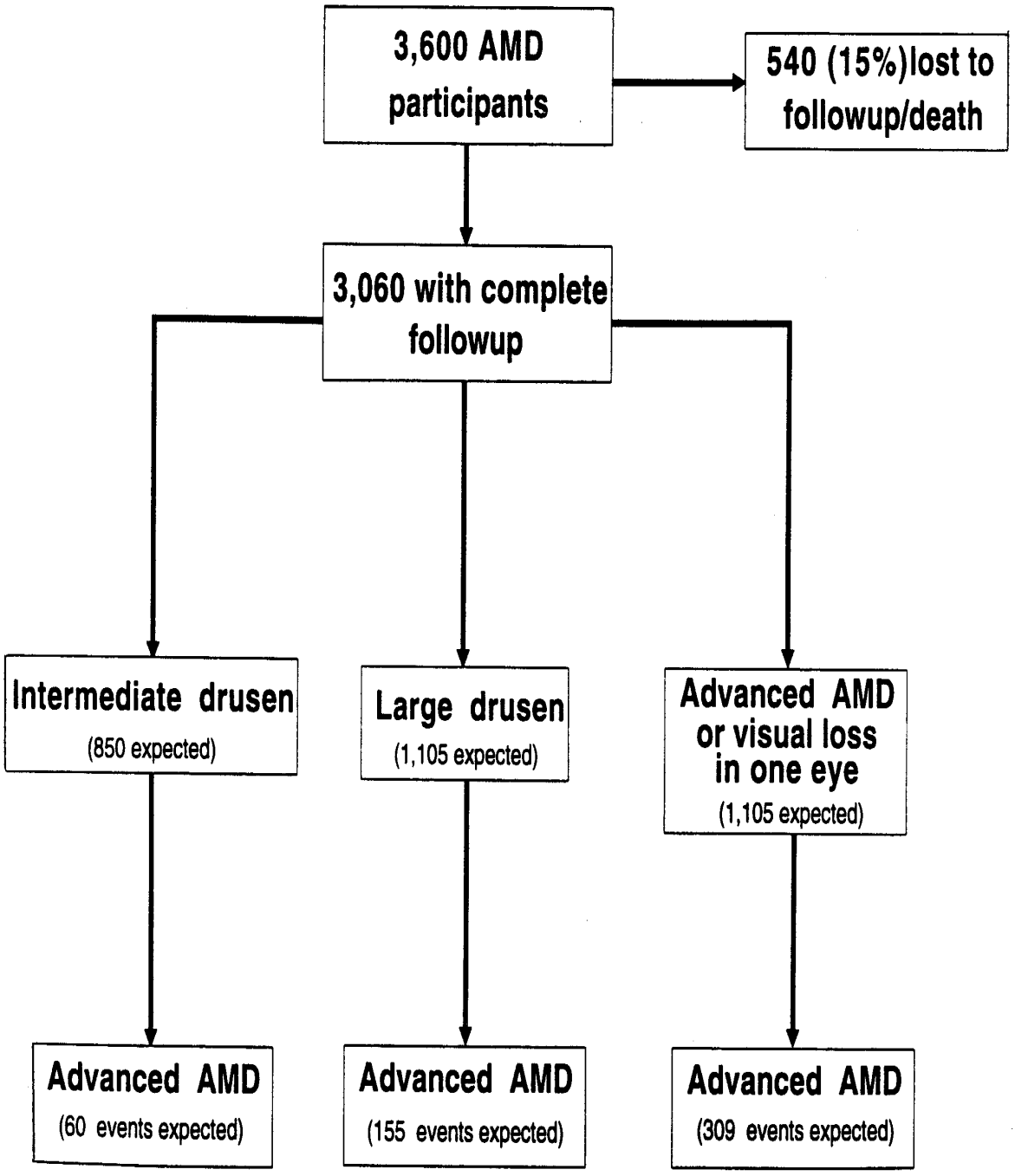


Exhibit 3-20. POWER ESTIMATES FOR PRIMARY STUDY OF AMD CLINICAL TRIAL

EVENT RATE = 0.17 n = 3,060

	Rates of Progression to Advanced AMD					
Situation*	Placebo (n = 765)	Antioxidants (n = 765)	Zinc (n = 765)	Antioxidants + zinc (n = 765)	Approximate power α = 0.05	α = 0.01
1	0.162	0.128	0.128	0.094	0.87	0.68
2	0.163	0.109	0.109	0.109	0.84	0.65
3	0.170	0.170	0.116	0.170	0.84	0.65
4	0.164	0.164	0.117	0.117	0.86	0.67

*

Situation	Percent reduction	Due to
1	25	Antioxidants
	25	Zinc
	50	Antioxidants and zinc (no interaction)
2	40	Antioxidants
	40	Zinc
	40	Antioxidants and zinc (negative interaction)
3	0	Antioxidants
	40	Zinc
	0	Antioxidants and zinc (negative interaction)
4	0	Antioxidants
	35	Zinc
	35	Antioxidants and zinc (no interaction)

Calculated for 3,600 participants with age-related macular changes; adjusted to 3,060 for losses to followup and deaths; rate of progression to advanced AMD of 0.17 is adjusted for nonadherence for each treatment group. Two-sided α.

Exhibit 3-21. POWER ESTIMATES FOR STUDY OF 2,600 CATEGORY 3 AND 4 PARTICIPANTS IN AMD CLINICAL TRIAL

EVENT RATE = 0.20 n = 2,200

	Rates of Progression to Advanced AMD					
Situation*	Placebo (n = 550)	Antioxidants (n = 550)	Zinc (n = 550)	Antioxidants + zinc (n = 550)	Approximate power α = 0.05	α = 0.01
1	0.19	0.15	0.15	0.11	0.80	0.63
2	0.192	0.128	0.128	0.128	0.79	0.58
3	0.20	0.20	0.136	0.20	0.79	0.58
4	0.193	0.193	0.137	0.137	0.80	0.60

*

Situation	Percent reduction	Due to
1	25	Antioxidants
	25	Zinc
	50	Antioxidants and zinc (no interaction)
2	40	Antioxidants
	40	Zinc
	40	Antioxidants and zinc (negative interaction)
3	0	Antioxidants
	40	Zinc
	0	Antioxidants and zinc (negative interaction)
4	0	Antioxidants
	35	Zinc
	35	Antioxidants and zinc (no interaction)

Note: Sample size is adjusted to 2,200 for losses to followup and deaths; rate of progression to advanced AMD of 0.20 is adjusted for nonadherence for each treatment group. Two-side α.

Exhibit 3-22. APPROXIMATE TREATMENT EFFECTS DETECTABLE WITH AT LEAST 90 PERCENT POWER BY PLACEBO EVENT RATE AND ANALYSIS GROUP FOR AMD TRIAL[1]

Analysis group	Sample size available[2] Number	Placebo event rate .50 Percent reduction	.30 Percent reduction	.20 Percent reduction
AMD (Category 2, 3, or 4)				
Total	3,060	20	25	30
Centrum®	1,836	25	30	40
No Centrum®	1,224	25	40	50
AMD (all participants)				
Total	3,910	15	25	30
Centrum®	2,346	20	30	35
No Centrum®	1,564	25	35	45

[1] Table assumes:

- No interaction
- Two-arm comparisons
- One-sided $\alpha = .025$
- 1 year treatment effect lag
- 15 percent loss to followup or death prior to event
- 60 percent choose to supplement with vitamins
- Drop-in rate 30 percent: 2 percent each of years 1 and 2, 4 percent each of years 3 and 4, 6 percent each of years 5, 6, and 7.
- Drop-out rate 20 percent: 2 percent year 1, 1 percent of year 2, 2 percent of year 3, 3 percent of year 4, 4 percent each of years 5, 6, and 7.

[2] Sample size adjusted for 15 percent losses to followup and deaths